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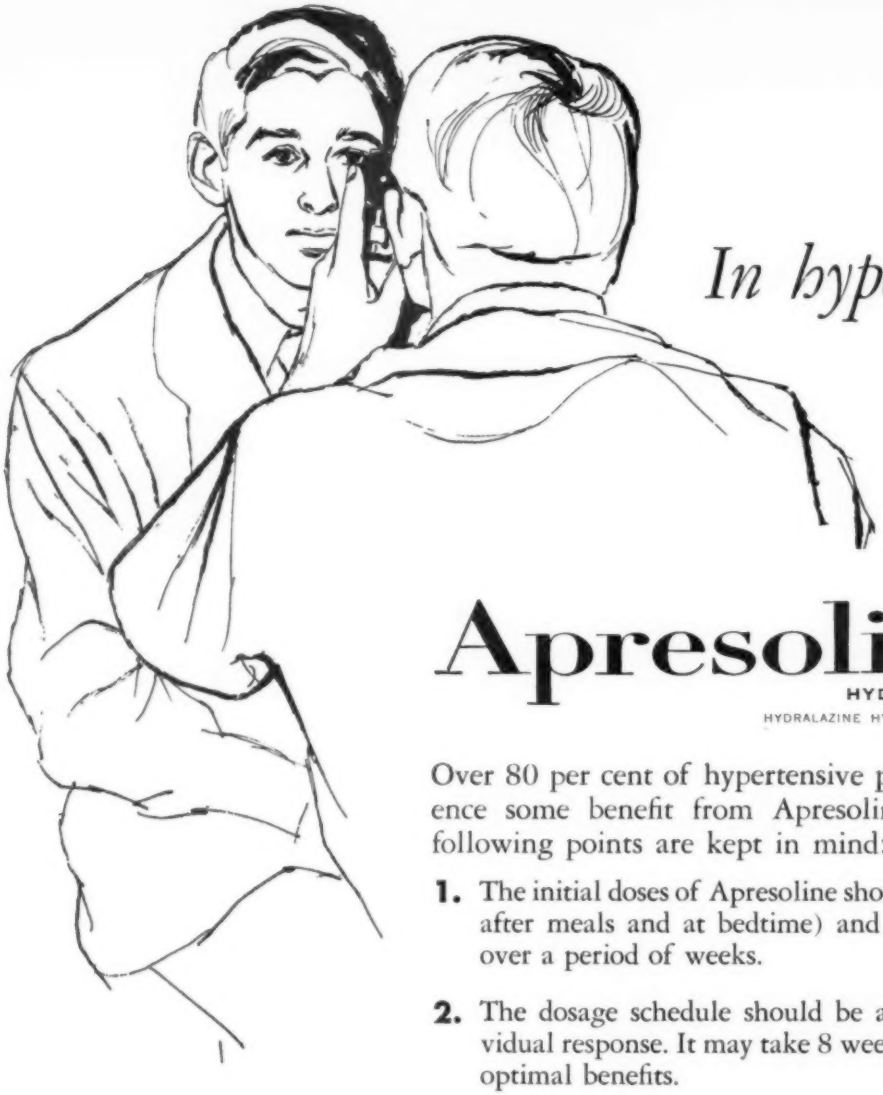

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THE PRESENT STATUS OF PLASMA SUBSTITUTES

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Ever since it became apparent to physicians that blood transfusion was an effective means of raising the arterial pressure of a patient in shock, attempts have been made to find blood substitutes that would achieve the same results. At first, most of the materials tried were ineffective or else produced a rise in blood pressure too transient to be of much value. Included among their number were various dextrose and saline solutions and such materials as gum acacia. In the early 1940's blood serum and blood plasma were heralded as the answer to the problem. It took but a brief experience in army hospitals in North Africa to prove that they could not take the place of whole blood in treating the shock induced by massive blood loss, but were, however, effective in combatting many forms of nonhemorrhagic shock. Since then plasma has been used only for the treatment of nonhemorrhagic shock and of hemorrhagic shock when no whole blood is available, for nutritional purposes, for the administration of immune bodies, and for the treatment of certain disorders such as hemophilia. With the discovery that homologous-serum hepatitis could be widely disseminated from pools of plasma infected with the virus, the use of plasma decreased rapidly. Partial control of the hepatitis by ultra-violet irradiation of the serum has not completely restored medical confidence in this material.

The outbreak of the Korean war in 1950 found us with very little plasma on hand. Immediately there was not only an urgent demand for plasma by the armed forces, but also the necessity of huge stockpiles in order to provide treatment for large numbers of casualties in case our cities should be subjected to atomic devastation. It is even now futile to think that we can accumulate and maintain plasma stockpiles in the amounts necessary for the protection of our own civilian population. Furthermore, plasma has certain inherent disadvantages beyond its potentialities of spreading hepatitis. It is costly to produce, it

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cannot be stored in the dried state at temperatures below freezing, because the accompanying solvent (water) will freeze. In the liquid or frozen state it is suitable only for hospital use. The reconstitution of dried or frozen plasma takes time and is difficult for the uninitiated.

It became obvious in 1950 that effective plasma substitutes which could be produced easily and cheaply would be necessary. England, Sweden and Germany, less fortunate than ourselves in that they had had little plasma in the past, were, because of this lack, years ahead of us in the development and use of substitutes. The foreign literature is abundant concerning the usefulness of these synthetic products and effusive in praise of their efficacy. The reports, however, are comparatively uncritical from the American viewpoint as to the injurious effects of these substitutes. For this reason it has been necessary not only to test the foreign materials which are in use, but also to make better products of our own and then submit them to exhaustive animal experimentation followed by clinical trial. Because of the time this has taken we are only now beginning to have some materials which have been sufficiently tested that they may be used clinically. Others, which are quite suitable and give promise of being better than those we now have, are still under investigation. There is also a last group of substitutes in only the first stages of development.

What is the most we can expect of a plasma substitute? The answer, certainly for the present, is that its colloidal osmotic effect should equal that of plasma in the restoration and maintenance of blood volume, arterial pressure and cardiac output, when used in treating shock; yet it should not have any untoward side effects. This result is achieved by the substitute having its molecular weight and viscosity adjusted so that it will not only restore blood pressure but will maintain it for a reasonable period of time. It is, of course, preferable to have a product which can be metabolized or one which can readily be excreted, but this is not essential as far as shock treatment is concerned. From the civil defense viewpoint, the availability of the material from which the plasma substitute is made is very important. So also are the expense of preparation, the stability of the product and the ease of its administration. Because we now have materials which in many respects approach these ideals, it is no longer necessary to regard as plasma substitutes the ordinary crystalloid solutions which are available in every hospital for intravenous therapy. They are used by all of us as a stopgap when no blood or plasma is available, but no one would elect to use them when more effective substances are at hand.

We must consider these materials one by one if we are to form a concept as to their value, since they vary considerably in their individual characteristics. Although many are in use in hospitals for experimental purposes, it is not yet possible for hospitals to obtain the quantities that they might wish. In examining these materials we should do so as clinicians, with an eye to what is acceptable at the present moment. There is little point in our discussing those materials which are still being investigated in the laboratory. Regardless of how promising they seem, until this promise is confirmed by adequate clinical trial they are but dreams and not reality.

PLASMA SUBSTITUTES

Serum albumin, derived from human plasma, exerts, in its undiluted salt-free form, five times the osmotic effect of plasma. The process whereby it is extracted is so effective in destroying the virus of serum hepatitis that no well substantiated case of transmission of the disease has been traced to this source (1). It is a stable liquid, easy to store, transport and dispense. It is completely free of the side effects attributable to other substitutes. It is readily metabolized. We have found it to be very effective in raising the serum protein levels of debilitated patients. It is available, however, in but small quantities, can only be produced slowly and is very expensive. Unless it is administered in a very dilute form or very slowly it can cause circulatory overloading by rapid withdrawal of fluid from the extracellular spaces. For this reason it cannot be recommended for use after a civilian disaster, as many of the victims would have cardio-respiratory reserves too inadequate to tolerate it. Its administration to old people can be dangerous if one is not familiar with its oncotic effect. Because of its effectiveness in small dosages it is ideal for military use in forward areas upon young healthy adults, particularly as expense seems to be of no concern to the government.

Globin, derived as a waste product from the red cells which remain when plasma has been withdrawn from whole blood, was developed by Dr. Strumia of Bryn Mawr (2). Its molecular weight is smaller than that of many of the other plasma expanders, so that in equivalent quantities it is less effective than many of the others. Furthermore, it will not maintain a restoration of arterial pressure for as long a time as is often desirable. It is relatively free of side effects, is non-infective and is nonantigenic. As it is readily metabolizable, it is useful in treating protein depletion. It is stored in the dried state and hence must be reconstituted with water before administration. It is, as yet, available only in small quantities and is more expensive than some other materials to produce. Experimental work is being conducted to render it more effective. Some workers have found globin to be an effective diuretic agent in the treatment of fluid accumulated in cirrhosis and nephrosis.

Gelatin has been used in many forms for a number of years. It is being made from animal bones and from pig hides, both types being presently available in a 5 or 6 per cent solution in saline or water. It is produced in various molecular sizes and called by various names, such as Plasmoid (Baxter), Travenol Gelatin (Baxter), Oxypolygelatin, Modified Fluid Gelatin and so forth. When first produced it was accused of having many untoward effects, but these reactions are not associated with the products that are now on the market. The molecular weight can be adjusted to give gelatin a colloidal osmotic effect comparable to that of plasma. In such a form it will maintain arterial pressure and blood volume for a satisfactory period of time. The retail price of Baxter's Travenol Gelatin is about $4.00 for 500 cc., so that it is relatively cheap; it gels below room temperature. Modified Fluid Gelatin remains fluid down to 4° Centigrade. Ravdin and his workers have found this material an effective blood volume expander when used in a small series of cases (3). Any material which gels below room temperature is suitable for use only in a warm hospital. Gelatin is noninfective,

is not antigenic, and is pyrogen-free. It is readily excreted by the kidney within twenty-four to forty-eight hours. Hartman (4) has reported transient nephrosis from its use, but Ravdin has not seen this complication in his series. It increases the sedimentation rate and hence can cause an appearance of false agglutination when blood typing and crossmatching are carried out by the microscopic technique. Supposedly, it sometimes increases venous pressure and can reduce the oxygen saturation of blood. In our hands this has not been a problem when gelatin is used in small amounts.

Dextran is a plasma substitute which has been used widely in Sweden and England. It is a glucose-polymer derived from beet sugar by the bacterial action of Leuconostoc mesenteroides. In its crude form it has a molecular weight of several millions. After purification and fractional hydrolysis, its molecular weight is adjusted to extend over a range of from 30,000 to 150,000—roughly that of plasma. Different laboratories have varied the mean molecular weight according to their own specifications. The molecules of low molecular weight leave the circulation through the kidney too rapidly to be of much value, whereas those of high molecular weight tend to be stored in the body, and theoretically can cause sludging. Exact control of molecular size within a narrow range is an expensive process for this material and other synthetic materials as well.

The Swedish product, Macrodex, and those manufactured in this country have been effective blood volume expanders (5). The main clinical problems arising from the use of this material have been the pyrogenicity of the imported product, toxicity and antigenicity. Although articles in the foreign literature have suggested that the reaction rate is very low, imported material has had a high rate of pyrogenicity in this country (6). The American material has been free of this trouble. A few rare toxic reactions have occurred. The antigenicity of the product is well substantiated both in animals and man. Studies in this country by Kabat (7) and others have shown that this can be a serious problem. Certainly such allergic reactions, if severe, are terrifying. We cannot say at present that these reactions can be eliminated. Theoretically, any person immunized against the organism used to degrade beet sugar into dextran, or against type 2 and type 20 pneumococci, typhoid bacillus, certain streptococci, certain salmonella and others, could have allergic reactions to this material. From the civil defense viewpoint this material has had several drawbacks to date, all of which are capable of rectification. The first is cost, the price being about $8.00 per 500 cc., retail. The second is the difficulty of producing batches of material of uniform molecular size. The third is the problem of producing it on the large scale desired. Dextran is capable of being metabolized (8). It leaves the body gradually unless its molecular weight is adjusted to a low range. There is some evidence of its causing tissue damage in animals (4).

Periston has a variety of names. It is known as Kollidon, Subtosan, Polyvinylpyrrolidone, PVP and by the proprietary name (Schenley) of PVP-Macrose. It was produced originally in Germany from acetylene by a polymerization process. During the last war over 500,000 units of it were dispensed in Germany. At first it was highly pyrogenic, but this complication has now been virtually

eliminated. The source of it in this country is from a large stockpile of the powdered material imported from Germany. It has been produced in the liquid form in a variety of molecular weights. The present material which the Schenley Company is supplying to the Federal Civil Defense Administration has a mean molecular weight of 50,000 with a range from 10,000 to a little over 100,000. It comes in a 3.5 per cent solution in physiologic saline. The American products are nonpyrogenic, noninfective, almost nontoxic and, as contrasted with dextran, nonantigenic. The mean molecular weight is not too difficult to control, but to produce it in a narrow range of molecular size so as to avoid loss through the kidneys as well as prolonged storage is expensive. PVP is not metabolized. Although perhaps 50 per cent of a moderate dosage will leave the body within three days, the excretion of the remainder may go on for several months. The best studies that have been carried on concerning body storage and excretion of gelatin, dextran and Periston have employed isotopes for tagging the materials. Gelatin can be deposited in the convoluted tubules of the kidney. Dextran is stored in small amounts in the reticulo-endothelial system, liver and lung. Periston is stored in much larger amounts in the reticulo-endothelial cells, liver, kidney, spleen and blood-vessel endothelium and the skin (4, 9). The degree of storage is dependent upon molecular size, amount administered and the span of time in which it is given. A safe rule in the past has been to limit the amounts of Periston given to an adult in a 24-hour period to 1500 cc. In the smaller molecular size in which it is now made, such limitations may not be necessary.

As of this date, Periston is the best blood volume expander for civil defense purposes. It is available in large quantities, it can be prepared rapidly and very cheaply, the finished product costing less than $2.00 for 500 cc. It is stable for prolonged storage. It does not gel or freeze as does gelatin, liquid plasma or the water accompanying dried plasma. It does not require reconstitution before administration as do globin, dried or frozen plasma. Its freedom from early side reactions renders it superior to dextran for administration by unskilled persons. It is ideal for use in civil defense aid stations and ambulances for treating shock of all kinds, until the patient can reach a place where whole blood is available. Although it may be improved and other substitutes may supplant it, because of its qualities Periston in its present form will always be useful.

DISCUSSION

From the viewpoint of the clinician, what is the place of the plasma substitutes in his therapeutic armamentarium? Which should he use? It is important to state again in this regard that whole blood is the only adequate material we have for treating shock that is secondary to hemorrhage. Plasma and plasma substitutes are useful in restoring blood volume, arterial pressure and cardiac output until whole blood can be obtained. In hospital usage, gelatin or Periston are satisfactory substitutes for this purpose. Dextran is useful but the possibility of its antigenicity and its greater expense render it less desirable. Serum albumin is dangerous for use in unskilled hands, particularly in treating old people, and is too expensive. Globin is effective if given in a larger volume than the other

materials, but is not yet available. The same reasoning applies to the use of these materials for treating nonhemorrhagic shock. Lundy has found plasma substitutes useful in treating hypotension in the operating room. If this hypotension is due to a diminished blood volume without a loss of red cells the use of these materials can be very effective, as we and others have found (10).

For treating shock in patients suffering from extensive burns which require large volumes of plasma substitutes, storage in the body becomes a problem. Therefore, irradiated plasma (or that obtained from small pools) would be a better choice than a substitute, partly because of its protein content. Gelatin would be the best plasma substitute for treating these patients, as it causes no tissue damage. Globin would have to be given in large quantities but possesses the advantage of being metabolized. Albumin, if its administration were properly controlled, would be good also. Because of the necessity for using large quantities of plasma volume expanders in treating burns, Periston and dextran would be more dangerous.

For the treatment of nutritional disorders in which depletion of the serum protein is a major factor, serum albumin, plasma and globin would be the only effective agents, in that order.

None of the plasma substitutes is effective for treating hemophilia or for transferring immunologic properties. Mention has been made of the affinity of Periston for bacterial toxins and other poisons. The possibility of using this material in a low molecular weight to carry poisons out of the body through the kidneys is an intriguing one.

It is well for all blood bankers to remember that synthetic materials such as gelatin, dextran and Periston cause increased red cell sedimentation, which may interfere with the reading of blood typings and crossmatchings carried out by the microscopic technique after large quantities of the materials have been administered. Hence the patient should have blood withdrawn for grouping and crossmatching before he receives much of these synthetic plasma substitutes.

One other material, still undergoing experimentation, which is interesting in its concept is the Stable Plasma Protein Solution of the Harvard Blood Fractionation Laboratory. This material was conceived with the idea of separating from plasma the clotting elements and the globulin fraction with its immunologic properties, by a cheap and rapid process. The resultant product is stable, can be stored in liquid form, is supposedly free of the virus of homologous serum jaundice, and is an effective blood volume expander, as well as being useful for providing protein intravenously. The separation of these materials fits in well with newer concepts of stockpiling and using specific elements of blood for specific therapeutic purposes.

Lastly, what of the future? This paper is but an interim report as far as plasma substitutes are concerned. Amino-acid polymers and various polysaccharides being investigated at present may prove to be more valuable substitutes than those we now have. Changes of the molecular size and improvement in manufacturing processes may render gelatin, globin, dextran and Periston far better in the future. Plasma substitutes are but in their infancy; when they

reach adulthood they will be cheaper, more effective, less dangerous and far more valuable to us all.

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PHYSIOLOGIC AND CLINICAL BASIS FOR THERAPY IN CHRONIC OCCLUSIVE ARTERIAL VASCULAR DISORDERS

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It has only been in recent years that the study of peripheral vascular disorders has emerged as a separate and distinct specialty. In the past, patients suffering from afflictions producing structural changes in the main arteries in the extremities were considered to be victims of an incurable malady. Such a view was based on the fact that in most instances the diagnosis was not made until the obliterative process was far advanced and, as a consequence, ulceration or gangrene was already present. However, as interest in the subject increased and a considerable amount of research in the physiology of the peripheral circulation took place (1), it soon became apparent that certain medical and surgical procedures could delay and even prevent the appearance of nutritional disturbances. At present the emphasis is primarily upon the early recognition of an arterial vascular disorder, at a time when the pathologic changes are still minimal or reversible and hence amenable to treatment. Amputation is no longer considered a natural and inevitable outcome of such a condition.

Therapy in the two most common occlusive arterial vascular disorders, thromboangiitis obliterans and arteriosclerosis obliterans, has a threefold purpose. The first is to increase walking ability; the second, to protect the involved limb from nutritional disturbances; and the third, to institute steps to preserve the viability of the remaining tissues and to facilitate healing of ulcers. An attempt has been made in the present report to evaluate the commonly accepted therapeutic procedures utilized in these three categories, on the basis of available physiologic and clinical evidence.

INTERMITTENT CLAUDICATION

The most frequent complaint of the patient with a chronic organic arterial vascular disorder is intermittent claudication, a finding which represents a discrepancy between the markedly increased metabolic needs of exercising muscles and the inadequate amount of nutrition brought to them through partially or almost completely occluded muscle blood vessels. Because of its prevalence, a great many measures have been suggested for the control of this symptom, among them being sympathectomy, sympatholytic drugs, abstinence from smoking, pancreatic extracts, and the use of mechanical procedures.

On the premise that sympathetic denervation of an extremity is followed by an increase in local blood flow, a number of studies have been carried out to determine the value of sympathectomy in the treatment of intermittent claudication

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(2). In most of these it was implied or concluded that this procedure increases walking ability, especially in the case of arteriosclerosis obliterans. However, a recent report (3) is not in accord with such a view. This investigation dealt with the results obtained in 58 patients with thromboangiitis obliterans and arteriosclerosis obliterans subjected to lumbar sympathectomy. Postoperatively, walking ability increased in 15 subjects, but in 10 of these the relief was only temporary, lasting for from several weeks to six months. When the group was studied from the point of view of whether the patients smoked or not, all 5 patients manifesting permanent improvement were found to be nonsmokers. The changes in claudication distance observed in a control series of 177 cases were considered to compare very favorably with those of the sympathectomized subjects. The patients in both groups who continued to smoke either showed no change, or a reduction in walking ability, whereas nonsmokers experienced no decrease and in many instances demonstrated an actual improvement in walking.

If the available physiologic evidence regarding the responses of blood vessels in the extremities is reviewed, the explanation for the foregoing findings becomes apparent. A considerable amount of data has accumulated recently to indicate that not all vascular beds in the limbs are under the control of the sympathetic nervous system (4). The use of various types of stimuli and chemicals which ordinarily cause an increase in vasomotor tone has revealed that the resulting reduction in local circulation is limited to the distal portions of the extremities (the hands and feet); at the same time no alteration or even an increase in blood flow occurs in the proximal portions (the forearms and legs). Since the latter are composed primarily of muscle, whereas skin predominates in the hands and feet, such evidence has been interpreted to indicate that the circulation through the skin can be considerably reduced by an augmentation in the number of vasoconstrictor impulses reaching the periphery, while that through the muscle vessels is not affected by such a change. Conversely, removal of sympathetic control over the peripheral blood vessels will result in a marked increase in blood flow through the skin, with no alteration occurring in the muscle circulation.

It is understandable, therefore, why intermittent claudication, which is due to an inability of muscle blood vessels to dilate sufficiently during exercise, should not be affected by sympathectomy. For the same reason, sympatholytic drugs or other procedures which remove vasomotor tonus have no value in the treatment of this symptom.

It is possible that some of the reported beneficial effects of sympathectomy on claudication distance (2) may have been due to other factors, such as the simultaneous institution of a regimen of abstinence from smoking (which is generally insisted upon), the psychic effects associated with an operation, and the response of the patient to the interest and solicitous attitude of his doctor. It is also important to point out that not infrequently the improvement in walking was found to be only temporary or, on the other hand, that it was first noticed as long as a year or more following the operation, at a time when a causal relationship was difficult to establish.

Another measure which has been studied with regard to its effect upon inter-

mittent claudication is the use of pancreatic extracts (Depropanex and Padutin). In the case of thromboangiitis obliterans, the available evidence would appear to indicate that little, if any, increase in claudication distance occurs following the intramuscular administration of these substances (3). However, in arteriosclerosis obliterans, definite improvement can be expected in more than half the cases thus treated (3, 5).

Abstinence from smoking appears to be a very potent factor in preventing progression of intermittent claudication in patients with thromboangiitis obliterans, and it may, in fact, actually increase walking ability (3). In arteriosclerosis obliterans, the evidence indicates that this therapy also has a beneficial effect, but not to the same extent as in thromboangiitis obliterans.

The various mechanical procedures, such as the Pavaex boot, intermittent venous occlusion, the oscillating bed, and Buerger's exercises have been used in the treatment of intermittent claudication, but attempts to evaluate their usefulness have not been successful. If one considers the physiologic evidence alone (6), there is little to support a claim that these measures in any way increase muscle blood flow. Until more definitive clinical data are presented, it would appear that such procedures have little place in increasing the walking ability of patients with thromboangiitis obliterans or arteriosclerosis obliterans.

PREVENTION OF NUTRITIONAL DISTURBANCES

With regard to the second approach to treatment, namely the prevention of nutritional disturbances, the aim of the therapeutic program is to protect the skin of the extremities. This involves 1) minimizing the possibility of injury to the tissues, 2) instituting measures which protect the limb from vasoconstricting stimuli, and 3) utilizing procedures which are capable of increasing local cutaneous blood flow.

Of greatest importance in the prevention of nutritional disturbances is the protection of the extremity from noxious agents. A rule that should always be followed in this regard is never to apply heat in any form to a limb with an impaired arterial blood supply. Neglect of this warning has been responsible for the loss of many extremities. A limb with a reduced circulation no longer possesses an effective mechanism for the removal of heat from its surface by means of the flow of blood through it. Hence the partially devitalized structures are exposed to the full effect of the injurious stimulus. Furthermore, the metabolism of the tissues is raised by the heat, but the mechanisms necessary to take care of the increased needs are inefficient, because of the impaired circulation. This produces an even greater discrepancy between metabolic requirements and the means to satisfy them.

There are a number of other noxious agents or procedures which may initiate nutritional changes and hence are likewise contraindicated. Strong antiseptics, like iodine or mercurochrome, and corn plasters should never be used, and fungus infections should be treated with mild measures. Application of pressure, as in the form of a tight cast, and forceful manipulation should not be attempted. In most instances adhesive tape should not be used on the skin, particularly if repeated applications on the same site are contemplated.

The extremity should at all times be protected from injury. If the patient has an occupation which exposes him to the hazards of trauma, then he should change his work. He should wear soft thick woolen socks and well-fitting shoes. Care should be taken in cutting the nails so that other tissues are not traumatized. Removal of corns or calluses or other surgical procedures should not be performed unless they are essential.

Vasoconstricting stimuli should be eliminated as much as possible. Exposure to cold is detrimental, because it decreases cutaneous blood flow, either through a direct and local effect of the cold on the limb, or as a result of reflex vasoconstriction following the application of cold to the rest of the body. The whole body and especially the feet and legs should, therefore, be warmly clothed during the winter months, and exposure to cold should be reduced to a minimum. Aside from its possible effect upon intermittent claudication, smoking has a proven vasoconstricting action upon cutaneous blood flow (7) and hence it should be forbidden on this score also.

The problem of whether removal of vasomotor tonus by sympathectomy will protect an extremity from nutritional disturbances has not as yet been answered. In the case of thromboangiitis obliterans, recent evidence indicates that the possibility of such a result is not great, particularly if the patient continues to smoke (3). In the case of arteriosclerosis obliterans, the procedure appears to have some protective action in this respect. With regard to the various sympatholytic drugs, there is little evidence that their prolonged use in chronic occlusive arterial vascular disorders will prevent nutritional disturbances.

ULCERS AND GANGRENE

In the case of the third approach to treatment, *i.e.*, the control of existing ulceration or gangrene, the early aim of the therapeutic program is prevention of spread of the nutritional disturbance to adjoining viable tissue. Simultaneously, steps should be taken to facilitate healing of the lesion, or, if the process is no longer reversible, to encourage a clear demarcation between living and dead structures, and thus allow for spontaneous or surgical removal of the necrotic material.

The arrest of the existing local infection contributes to both purposes of the therapeutic program. There is little question that inflammation, if left uncontrolled, will cause thrombosis of the small vessels in the tissues close to the nutritional disturbance and so lead to an extension of the anoxic process into this area. Furthermore, the presence of infection inhibits any reparative attempts to epithelialize an ulceration. It is, therefore, essential to place the patient at complete bed rest and to determine the type or types of organisms present in the lesion, so as to utilize the most effective means of destroying them. To accomplish this, it is necessary to make a culture of secretion from the ulcer base and then ascertain the relative sensitivities of the bacteria to antibiotics. When such information is available, the proper medications should be administered locally and parenterally. Dressings should be bland, nongreasy and nonallergenic.

Before local application of antibiotics can be made effective, it is necessary

to remove eschars and necrotic tissue in order to permit the therapeutic action of the ointments to be exerted directly on the ulcer base. Although this can at times be accomplished with little difficulty, in most instances preliminary softening of the material is necessary. For this purpose, such agents as Dakin's solution, azochloramide in oil and the more recently described substances, Varidase and Tryptar, may be tried. The latter two do not appear to have any great advantage over the others. If deep pus is present, it should be drained, this step at times necessitating open amputation of a gangrenous toe, together with a more proximal incision.

Since an increase in local blood should inhibit spread of the process and also facilitate healing, it appears worthwhile to use procedures which cause such a response. In this regard, sympathetic denervation provides a ready therapeutic means of augmenting blood flow through cutaneous arteries, inasmuch as elimination of vasoconstrictor impulses is followed by passive relaxation of these vessels. All the measures used for this purpose either produce temporary or permanent destruction of the pathway of the sympathetic nervous system somewhere in its course, or inhibit the number of vasoconstricting impulses arising in the vasomotor center. Among those which temporarily prevent vasomotor impulses from reaching the peripheral blood vessels are paravertebral sympathetic block with procaine, and the use of sympatholytic drugs. Of the latter, the best known are Etamon, Dibenzyline, Priscoline, and Hydergine. Etamon has a blocking effect on all autonomic ganglia, parasympathetic as well as sympathetic, whereas Dibenzyline blocks the action of sympathin E and epinephrine at the neuroeffector organ in the blood vessel wall by combining with the excitatory adrenergic receptor substance. In the case of Priscoline and Hydergine, the site of action has not been clearly defined, although it is probably also at the periphery.

Among the procedures which reduce the number of impulses arising in the vasomotor centers is that of indirect vasodilatation, produced either by the application of heat to distant portions of the body, or by the use of vaccines, to raise systemic temperature. Under both circumstances, the temperature-regulating centers in the hypothalamus are stimulated and, as a result, impulses are sent down to the vasomotor centers, inhibiting the rate of formation of constrictor impulses. Use of oral whiskey has a similar effect, and the intravenous administration of procaine (1000 cc. of 0.1 per cent solution) has the added advantage of controlling the associated pain through its anesthetic properties.

Although there is agreement on the value of the foregoing measures in increasing cutaneous blood flow in the presence of nutritional disturbances, there is no unanimity with respect to whether such a procedure as sympathectomy is warranted under these circumstances. This subject was investigated in a recent study (3) in which 30 limbs of patients suffering from thromboangiitis obliterans or arteriosclerosis obliterans were sympathectomized because of the presence of ulcers or gangrene limited to the toes. Early healing took place in 18 extremities, but in 5 there was a delay of several months to a year. In 7 (23.3 per cent), nonhealing resulted or the limb had to be sacrificed. With conservative therapy,

early healing occurred in 61 of 124 extremities, but in 8 it was delayed for several months. In 55 instances (44.4 per cent) nonhealing occurred, or the limb had to be amputated. It was pointed out, however, that whereas the sympathectomies were performed only on limbs in which the ulcer or gangrene was limited to a toe or toes, in the control groups the lesions had frequently progressed to involvement of the foot proper before adequate therapy was instituted.

SUMMARY AND CONCLUSIONS

On the basis of available physiologic and clinical evidence, it would appear that the generally accepted therapies in thromboangiitis obliterans and arteriosclerosis obliterans are only of limited value. Most of them have certain disadvantages and many of them are only partly successful in accomplishing a persistent increase in peripheral blood flow. It is through the use of proper combinations of the therapeutic tools that improvement can be expected.

With regard to the control of intermittent claudication, sympathectomy and the sympatholytic drugs appear to have little or no beneficial effect. Abstinence from smoking plays a much more important role in this respect in thromboangiitis obliterans and has a definite but less marked therapeutic action in arteriosclerosis obliterans. The pancreatic extracts are worthy of a clinical trial in the latter condition but not in thromboangiitis obliterans.

In the prevention of nutritional disturbances, the local care of the feet is paramount. Particularly contraindicated are exposure to heat and extreme cold and trauma, spontaneously or surgically incurred. Prophylactic sympathectomy in thromboangiitis obliterans is not warranted, since it will not necessarily protect the limb from future nutritional changes, particularly if the patient continues to smoke. In the case of arteriosclerosis obliterans, this procedure may have some protective action. Abstinence from smoking appears to play an important role in preventing the onset of ulcers or gangrene in both types of chronic occlusive arterial vascular disorders.

In the treatment of nutritional disturbances, the control of infection and the removal of necrotic tissue are essential. Temporary inhibition of vasomotor tonus, so as to increase cutaneous blood flow, is also beneficial in the healing of the lesion. Permanent denervation, as through sympathectomy, appears to lead to fewer amputations than does conservative therapy. The procedure, however, should be limited to those cases in which the gangrenous or ulcerative process has not as yet involved the foot proper.

With a minimum of medical supervision, most patients with arteriosclerosis obliterans and thromboangiitis obliterans should be able to live a fairly normal, although somewhat physically restricted, life. Death, when it occurs in such individuals, can generally be attributed to some factor other than the pathologic process in the extremities.

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TREATMENT OF HYPERTENSION IN ELDERLY PATIENTS WITH METHIUM CHLORIDE

Preliminary Report

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Malignant hypertension is very often fatal in youth or middle-aged patients, but occurs rarely in old age. On the other hand, there are more benign forms of hypertension with various degrees of deleterious effects on the heart or the blood vessels, the incidence of which increases in number steadily to a moderately advanced age, such as 75 (1). In the elderly, arteriosclerotic and atherosclerotic changes usually result in systolic hypertension, often with little or no increase in the diastolic pressure. The resulting high pulse pressure more frequently is apt to lead to cerebral hemorrhage than to heart failure.

The main problem of hypertension is presented by the large group of hypertensive patients intermediate between those with the malignant form in the earlier age groups and those with the arteriosclerotic form (1). Many older persons with hypertension have, as a rule, reached an age at which there is less severe nervous and physical strain than they had been subjected to ten to twenty years earlier. Apparently they can more easily adjust themselves to a life of decreased activity better suited to hypertensive strain, and therefore can carry on usefully and comfortably.

These older patients frequently are allowed to go untreated, since it seems needless to subject them to the rigors of the rice diet, the low-sodium diet, or the possible undesirable side effects of the more potent recently introduced hypotensive drugs. Furthermore, they are not suitable subjects for sympathectomy. If a potent hypotensive drug is used, there is always the fear that a coronary or cerebral accident may be precipitated in elderly patients. As a result, general supportive measures are prescribed without any specific attempt to lower blood pressure. To the best of our knowledge, no drugs previously recommended as hypotensive agents have been particularly successful in lowering blood pressure in patients in the advanced age range.

Numerous favorable reports have been published on the usefulness of the hexamethonium salts for the lowering of blood pressure (2–5). The earlier work was carried out primarily with injectable hexamethonium and several investigators with wide experience still believe that this is the drug of choice (6–8).

When Methium[1] (hexamethonium chloride) was made available for oral use it seemed advantageous to determine whether it might be of some value in elderly hypertensive patients. Methium offered the advantages of being effective orally

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[1] Methium Chloride was supplied by the Warner-Chilcott Laboratories.

and also free from the possibility of bromidism, associated with oral use of the bromide salt (2). Frankly, when this study was undertaken, little response to Methium was anticipated, since the patients represented primarily a group with arteriosclerotic hypertension. It has been believed that the arteriosclerotic vascular system cannot respond adequately to ganglionic blocking agents such as hexamethonium.

TABLE 1

CASE NO.	Patient	Sex	Age	Blood pressure before treatment (mm. Hg)	Blood pressure on last day of medication (mm. Hg)	Duration of medication (days)
1	A. B.	M	76	180/145	148/68	52
2	S. B.	M	93	180/80	140/70	52
3	M. C.	M	77	190/78	160/80	52
4	F. H.	M	72	164/68	132/68	20
5	M. F.	M	85	208/75	210/84	60
6	S. D.	M	77	212/130	215/115	40
7	M. F.	M	90	218/90	162/74	60
8	H. F.	M	90	180/78	158/65	37
9	G. F.	M	83	238/78	178/58	37
10	J. G.	M	68	170/78	128/67	30
11	S. G.	M	70	168/78	148/76	20
12	I. G.	M	84	174/64	158/65	21
13	L. G.	M	80	180/88	198/88	21
14	F. A.	F	83	200/72	160/68	40
15	G. B.	F	68	205/95	148/76	35
16	B. B.	F	73	190/70	164/64	35
17	J. B.	F	81	210/84	180/80	30
18	B. W.	F	83	220/78	208/80	30
19	A. S.	F	86	200/100	210/100	30
20	D. P.	F	74	190/90	168/78	30
21	B. G.	F	72	200/90	176/88	14
22	F. G.	M	67	220/100	190/90	30
23	J. W.	M	66	206/98	159/85	27

METHOD OF STUDY

The patients for study were selected from those who were housed at the Home and Hospital of the Daughters of Jacob and who were, therefore, living in a more or less controlled environment. It was felt that the observations on the patients' response, progress and control of medication could be easily followed.

Twenty-three patients whose age range was from 65 to 90 years were selected for study. There were 15 males and 8 females. They were not given any special diet. There had been a significant number of blood pressure readings taken prior to the use of Methium, so that average readings for each patient were well known. These ranged from 164/68 to 238/78 mm. of Hg.

Therapy was initiated in all patients with a dose of one 125-mg. tablet of Methium per day. The blood pressure readings were recorded at periodic intervals. If the initial dose was well tolerated, it was elevated to as much as 375

mg. daily. The optimal dose was determined for each patient in this manner. At this stage of the study the lowest effective daily dose was found to be 125 mg., and the highest 375 mg. The average dosage which was found to be efficacious was 250 mg. per day.

The patients received this medication for from fourteen to sixty-two days (Table 1). Complete blood counts, urine examinations and determinations of the blood urea nitrogen level were made before treatment and at periodic intervals after therapy was started.

RESULTS

The results in this preliminary study were unusually gratifying, especially since little effect had been anticipated. All but 6 of the 23 patients showed a satisfactory reduction in blood pressure, with relief of the symptoms in most of the patients.

It is not easy to evaluate subjective symptoms in elderly people. However, certain objective findings were noted. For example, 1 aged subject discarded his cane because he felt his eyesight had improved. Another was not so irritable and seemed to get along much better with the other patients. One woman who became dizzy and thought she would fall when she looked toward the ceiling lost these symptoms while taking Methium. Other aged subjects still complained of headaches, dizziness and insomnia, although the blood pressure was reduced. In elderly individuals it is difficult to state whether these symptoms are due to hypertension, constipation or psychogenic factors associated with aging.

One patient died of a cerebral vascular accident during the course of this study. This man had a blood pressure of 180/80 before treatment; after twenty-one days of therapy the blood pressure was 198/88 when he succumbed. In our opinion this fatality had no relationship to the therapy. In most of the patients, with the dosage employed, it was possible to reduce the systolic blood pressure by an amount ranging from 18 to 60 mm. of Hg. No attempt was made to give sufficient Methium to reduce the blood pressure to normotensive levels, since this was thought to be unwise in patients of advanced years.

Side effects with hexamethonium are an inevitable result of the drug's action, since it blocks not only the ganglia causing vasoconstriction but all the ganglia of the autonomic nervous system. The most commonly noted side effects in order of severity and frequency were constipation, blurring of vision and difficulty in starting urination (2). Postural hypotension is not considered a side effect by some investigators, but is evidence that hexamethonium is effective (2).

In this series the side effects were not troublesome. In prescribing Methium we observed that it was best to start with a comparatively small dose and gradually increase it. We followed this procedure because in 1 patient who had a blood pressure of 206/110 before therapy was instituted, the blood pressure dropped to 130/90 after 62.5 mg. of Methium. The medication was stopped for two days and then started again with a similar dose. This time the blood pressure dropped to 150/90, and upon a maintenance dose of 125 mg. a day it remained around 159/90.

COMMENTS

This preliminary report admittedly deals with a small series of cases, without a control group. Also this study does not take into consideration spontaneous reductions in blood pressure, improvement in the elderly hypertensive patient which may result from extra attention, or the psychogenic factors which frequently contribute to or may be a large factor in essential hypertension at all ages. The results obtained, however, were so contrary to those anticipated, based on theoretical grounds and previous experience, that it seemed worthwhile to report these early findings.

The satisfactory relief of the abnormally high pressures and the removal of the patient from the dangerous range of hypertension were impressive. The findings suggest that a more positive approach to relieving the symptoms and controlling the blood pressure in the elderly hypertensive patient, is possible and practical. If these results are substantiated, it seems reasonable to conclude that the arteriosclerotic patient can benefit from this new potent hypotensive drug. It certainly deserves further careful evaluation in elderly hypertensive patients, previously allowed to go untreated.

The present study is being continued. An additional series of patients will be treated with Methium and the results will be compared with the findings in a control group of subjects in the same age range who are given placebos.

CONCLUSION

1. Methium Chloride (hexamethonium chloride) has been administered orally to a group of 23 elderly hypertensive patients, in the age range from 65 to 90 years.

2. Results were most gratifying in all but 6 of the patients.

3. Comparatively few side effects from the use of the drug were observed in this series.

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MODULATED LAXATIVE ACTION FOR THE GERIATRIC PATIENT

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It is generally agreed (1–4) that many elderly patients take laxatives and that it is unwise to insist on their discontinuance. This report is an attempt to outline the problem and the type of work required to provide a rational answer to the following questions: "Why do elderly patients take laxatives?" "Why is it wise not to insist on discontinuance?" "What laxative should be recommended for an elderly patient?"

The results of an initial study are reported.

CHRONIC CONSTIPATION IN THE ELDERLY

Difficulty with defecation among elderly patients may arise from any one of several different mechanisms or combinations thereof:

1. Loss, diminution, or suppression of normal colonic reflexes.
2. Insufficient bulk to excite the normal reflexes and physiologic mechanisms of the intestine.
3. An atonic bowel.

An understanding of the mechanisms at fault in chronic constipation is possible by the use of modern pharmacologic and physiologic methods. Stimulation and recording of rectal and colonic activity by means of multiple balloons (the type generally used in studying duodenal activity) in conjunction with administration of sympathetic and parasympathetic inhibitors and stimulators, as well as direct muscle stimulants, may help to elucidate the problem.

It is generally agreed that if a patient can do without laxatives he should do so, but the doctor should not *insist* that *every* patient give up laxatives. Hardy (5) has pointed out, "The regular use of an aperient is surely to be judged by its effect on colon function. If it assists that function as defined in this lecture, well and good, but if it causes pain, wind, looseness of the stools or the passage of mucus . . . it is to be condemned."

Gainsborough (6) has said, "However, despite such measures, a recourse to drugs is often necessary either temporarily or for long periods, and a knowledge of the pharmacological action of the various preparations is essential for their correct use." Most doctors try to discontinue use of all laxatives and, failing in this, try to shift the patients from irritant or stimulant laxatives to bulk laxatives; but this is not always possible. It appears that stimulant laxatives produce, in some patients, a desirable therapeutic effect which cannot be duplicated by any other measures. To quote Soper (7), "The severe type of hypotonic colon

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requires some sort of stimulant. The extract of cascara sagrada, from 10–30 drops given before each meal, is very effective." According to Streicher (8), "If the simple procedures do not correct the condition it becomes necessary to resort to medications; it may seem that laxatives may be utilized only temporarily, but the extreme chronic obstipation may commit one to a habitual use of a minimum requirement." In discussing the use of laxatives Winkelstein (9) states, "Irritant laxatives are needed for the aged with flaccid abdominal walls, after pregnancy and abdominal operations, and when non-irritant laxatives fail." Heilbrun (10) has reported in great detail the case of a 36-year-old woman who, despite intensive therapeutic measures, was unable to obtain either complete freedom from symptoms or the feeling that her bowels were adequately emptied, except through the use of stimulant cathartics. Marks (11), in the course of studying colloid laxatives in elderly patients, found that the addition of a stimulant laxative was necessary to produce effective results.

It would thus appear unwise to *insist* on the discontinuance of laxative medication in the elderly, since such medication in some cases produces a desirable therapeutic result which cannot be achieved by any other measures.

In answer to the question, "What laxatives should be recommended for an elderly patient?" it is apparent that a laxative regimen should be used which most nearly restores to normal the basic physiologic defect causing constipation.

In a search for laxatives to recommend on the basis of mildness of action, the present study was undertaken of a commercial laxative preparation containing cascara sagrada, phenolphthalein, bile salts and papain, all present in relatively small amounts per tablet. The plan of the study was to administer each of the first two principle laxative ingredients to the patients separately in tablets that could not be distinguished by appearance or taste from the commercial preparation. If the laxative action was due mainly to either of these ingredients alone, there would be no reason to recommend the compound tablet. If the action was due to the additive or potentiated action of several of the ingredients, the modified nature of the resultant responses would need to be evaluated.

METHOD OF STUDY

The study was conducted in a home for the aged, on 55 elderly patients (39 men and 16 women) having a median age of 65.5 years. Patients were selected whose case histories revealed constipation persisting at least three years, and who had no evidence of a gastrointestinal pathologic condition. In this group there were 9 controlled diabetics, 2 syphilitics, and 25 patients with mild cardiovascular disorders. Of the 55 patients who started the test, 50 completed it. One was removed from the study because of intercurrent illness not related to the medication, and 4 because of refusals to continue medication. All of the patients were taking laxatives in one form or another at the start of the study. All medicaments were discontinued, with the exception of multi-vitamins, insulin, and penicillin when indicated. The diets for the groups were identical and designed to supply between 2,000 and 2,500 calories daily. Since it was difficult to control the liquid intake of the patients, this was not attempted, and the

patients were simply encouraged to drink plenty of water. Activity and exercise were not altered in any way.

The patients were first given placebo tablets for a two-day period. Then there was substituted one of the tablets being tested (*i.e.*, cascara sagrada or phenolphthalein, or a combination of the two, or the laxative compound tablet) for a three-day period. Placebos were again administered for four days, followed by another one of the tablets being tested. The procedure was repeated during the entire test period (five weeks or 1,750 patient-days, of which 750 were medication days). Patients who complained of not defecating for two days were evacuated by means of enemas; otherwise they were allowed to go four days before receiving an enema. Two days were allowed to pass after the enema before the test routine was reinstituted.

To minimize subjective influence as much as possible, neither the staff nor the patients knew of the identity of the test preparations and only the senior medical residents were aware of the nature of the study. All of the patients were accustomed to taking tablets daily of one sort or another to overcome their constipation, so that the tests did not subjectively or otherwise upset their established routines.

Each patient was questioned regarding consistency of the stool, ease of passage, incidence of cramps, griping, flatulence, nausea, and general sense of well being. To prevent any psychologic effects, this type of questioning was begun two weeks prior to the start of the study.

Patients who were not part of the study, but who were receiving other daily medication, were also questioned in such a way that the patients in the medication series would not attach undue importance to the procedure. Each patient served as his own control, since all received each of the test preparations and the placebo tablets. All the stools of 10 patients chosen at random were analyzed for water content and weight, as a further measure of the degree of laxation obtained.

RESULTS

Table 1 shows the laxative effects obtained when the principal components of the commercial tablet[1] were tested, first separately, and then in combination. Bile salts and papain in the doses used in the commercial preparation are not known to have any laxative action by themselves, and hence were not tested separately. *The compound preparation had a much greater laxative effect than the individual or combined actions of the two principal laxative ingredients* (cascara sagrada, and phenolphthalein). This is easily perceived in Table 1 when comparing the results with medication regimens 4 and 5. It should be noted that the number of tablets per day was essentially the same for all medication regimens. For statistical analysis all data were corrected to correspond to 150 patient-days of medication.

In Table 1, under the column headed "stools per day," it will be noted that the average number of stools per day was 0.21 for the placebo, and 0.23, 0.26,

[1] Caroid® and Bile Salts with Phenolphthalein.

and 0.13, respectively, for regimens 2, 3, and 4. There are no statistically or clinically significant differences between these four values or the corresponding ratios of days without stools to days with one or two stools. Statistically, the probability is only 1:1000 that regimen 5 would produce the distribution of stool frequencies observed, if it were no different from the other medications. Thus the laxative compound tablet produced a definite laxative action, whereas its individual ingredients did not, as far as numbers of stools per day were concerned.

When one considers the stool consistency data, it appears that cascara sagrada and phenolphthalein separately tended to produce looser (though not more) stools than lactose. To test the statistical significance of this, one can assume that lactose, cascara sagrada and phenolphthalein should produce the same

TABLE 1

	Total patient-days	Tablets per day				Stools per day					Stool consistency			Days of watery stools	Patients with watery stools	Defecation		Patients given enemas	Patients given add'l laxatives
		2	4	6	Avge.	0	1	2	3	Avge.	Watery	Soft	Hard			Easy	Difficult		
1. Lactose	147	2	137	8	4.08	118	27	2	0	0.21	0	11	20	0	0	8	23	20	3
2. Cascara sagrada, 0.048 Gm.	148	3	141	4	4.01	117	28	3	0	0.23	7	7	20	4	4	13	21	23	2
3. Phenolphthalein, 0.032 Gm.	139	0	135	4	4.06	109	25	4	1	0.26	11	10	15	4	4	19	17	17	4
4. Cascara sagrada, 0.048 Gm., phenolphthalein, 0.032 Gm.	136	6	128	2	3.94	119	16	1	0	0.13	0	4	14	0	0	4	14	27	2
*5. Cascara sagrada, 0.048 Gm., phenolphthalein, 0.032 Gm., bile salts compound, 0.080 Gm., papain, 0.10 Gm.	150	11	138	1	3.87	27	85	38	0	1.07	11	142	8	7	5	156	5	2	0

* Medication 5 was in the form of tablets of commercial Caroid® and Bile Salts with Phenolphthalein.

pattern of stool consistency. One can then test the data for homogeneity, using the Chi-square test of goodness of fit between expected and actual frequencies. Table 2 presents this analysis of the comparison between lactose, cascara sagrada and phenolphthalein. There was no significant difference between the consistency with cascara sagrada and phenolphthalein ($P - 0.3$), but lactose had a different pattern, of statistically probative value. Hence the effect of cascara and phenolphthalein in shifting to more liquid stools was beyond the probable magnitude of chance variation.

The last two columns in Table 1 present the data on the laxative effect of the various medications in terms of patients in whom the laxative was ineffective, *i.e.*, those who felt they needed more assistance than given by the test medication. Although cascara sagrada and phenolphthalein alone had a moderate laxative effect, as seen from an analysis of stool consistency data, they were inade-

quately effective as far as the patients were concerned. As great a number of patients required additional laxatives or enemas while taking cascara sagrada or phenolphthalein as when taking the control lactose. In addition, the combination of cascara sagrada and phenolphthalein in the dosage used even appeared to be slightly constipating. In marked contrast, the laxative compound tablets produced a very satisfactory effect from the patient's point of view. This was shown by the fact that only two enemas and no supplementary laxative at all were called for in 150 patient-days. Statistical analysis by the binomial distribution of the data in these last columns of Table 1 reveals that the results with this compound tablet offer less than one chance out of a hundred of being accidental.

Table 3 shows the subjective responses of the patients to the various medication regimens. Four categories of side reactions were recorded—cramps, griping,

TABLE 2

Sample of Variance Analysis on Stool Consistency Data

Medication	*Actual frequencies*, corrected for relative number of medication days				*Expected frequencies*, if the proportion of watery, soft, and hard stools is the same in all groups			
	Watery	Soft	Hard	Totals	Watery	Soft	Hard	Totals
Lactose	0	11.22	20.41	31.63	5.72	8.77	17.14	31.63
Cascara sagrada	7.09	7.09	20.27	34.45	6.22	9.56	18.67	34.45
Phenolphthalein	11.87	10.79	16.19	38.85	7.02	10.78	21.05	38.85
Total	*18.96*	*29.10*	*56.87*	*104.93*	*18.96*	*29.11*	*56.86*	*104.93*

$Chi^2 = 13.03$ = sum of the difference between actual and expected frequencies squared and divided by the expected frequency.

N = 4 = degrees of freedom.

P = 0.01 = One chance in a hundred that the actual distribution of stool consistencies would have occurred on a random basis if the proportion of watery, soft, and hard stools was the same for all three medications.

flatulence, and nausea. The laxative compound tablets were effective in reducing the incidence of all these symptomatic manifestations. The differences between this compound tablet and the other medications were statistically significant for all four types of side reactions. Considering the slight and moderate side reactions separately, similar results were obtained except in the case of moderate griping reactions, but the statistical significance was doubtful. Comparison of results with the laxative compound tablet in the combined (slight and moderate) data with the average of results with the other four medications, shows that the compound tablets reduced the incidence of cramps 4-fold, the incidence of griping 3-fold, the incidence of flatulence 4.4-fold, and the incidence of nausea 6.5-fold, in spite of their having *increased* the number of stools to 5 times those of the control regimens.

The combined form of medication reduced the total number of side reactions and also greatly improved the patients' sense of well being. There is a marked,

dramatic, and statistically significant difference between the laxative compound tablet and the other medications for each category (good, fair, and poor). It is especially worthwhile to note that the proportion of good, fair and poor days was essentially the same when the patients were: a) without laxatives, b) taking cascara sagrada, c) taking phenolphthalein, or d) taking cascara sagrada and

TABLE 3

Medication	Total days of medication	Days of gastrointestinal distress								Sense of well-being by days		
		Cramps		Griping		Flatulence		Nausea				
		Slight	Mod.	Slight	Mod.	Slight	Mod.	Slight	Mod.	Good	Fair	Poor
1. Lactose	147	59	6	60	2	73	21	6	1	23	58	66
2. Cascara sagrada, 0.048 Gm.	148	37	11	68	5	96	17	5	0	27	72	49
3. Phenolphthalein, 0.032 Gm.	139	50	8	67	7	67	22	9	0	24	57	58
4. Cascara sagrada, 0.048 Gm., phenolphthalein, 0.032 Gm.	137	30	6	57	6	65	16	6	0	26	65	46
5. Cascara sagrada, 0.048 Gm., phenolphthalein, 0.032 Gm., bile salts compound, 0.080 Gm., papain, 0.10 Gm.	150	12	1	21	1	22	2	1	0	122	23	5

TABLE 4

*Physical Properties of Stools**

Medication (tablet)	Mean weight (Gm.)	Mean water content (%)
None (control period before medication)	105.6	74.3
1. Lactose	107.3	73.5
2. Cascara sagrada, 0.048 Gm. (U. S. P. extract)	112.2	75.2
3. Phenolphthalein, 0.032 Gm	116.3	76.3
4. Cascara sagrada, 0.048 Gm. (U. S. P. extract), phenolphthalein, 0.032 Gm	123.4	79.8
5. Cascara sagrada, 0.048 Gm. (U. S. P. extract), phenolphthalein, 0.032 Gm., bile salts compound, 0.080 Gm., papain, 0.10 Gm.	153.8	78.3

* Derived from quantitative collection of the stools of 10 patients.

phenolphthalein in these dosages. In considering the subjective data on the sense of well being, it is important to remember that at no time did the patients or interviewers know what medication was being given. It must be concluded that the laxative compound tablets had a "tonic" action mirrored in the better subjective condition of the patient. Whether this "tonic" action is related to the laxative effect or to an independent phenomenon is a matter of conjecture, but its importance cannot be minimized for a group of geriatric patients.

The results obtained in an analysis of weight and water content of all the stools from 10 patients selected at random are summarized in Table 4. This table shows a significant increase in the mean weight of the stools of the patients receiving the laxative compound tablets, with no significant change in the mean water content.

DISCUSSION

The increase in the number of stools after laxative compound tablets, compared with the number after cascara sagrada and phenolphthalein separately, is of particular interest in view of the results obtained by McGuigan, Steigmann and Dyniewicz (12) who studied the dose-response curves of cascara sagrada and phenolphthalein in man. These authors observed that in normal patients 0.06 Gm. of phenolphthalein produced a laxative effect in 44 per cent of the patients; 0.1 Gm. in 63 per cent, and 0.2 Gm. in 74 per cent. [This was in normal subjects, and a laxative effect was considered to be an increase in the number of stools or a change in consistency.] Constipated patients gave the same general type of response as the normal subjects, but chronically constipated patients were somewhat less sensitive to the laxative effect of phenolphthalein. These same authors also noted that 2 cc. of aromatic fluid extract of cascara sagrada (which corresponds to 0.30 Gm. of the material used in this study) produced a laxative effect in 44 per cent of normal subjects and 4 cc. produced a laxative effect in 66 per cent.

Since doubling the dose of phenolphthalein increased the laxative response from 44 per cent to 63 per cent, and doubling the dose of cascara sagrada increased the laxative response from 44 per cent to 66 per cent, the respective doses of phenolphthalein and cascara sagrada used are equivalent and the two compounds have essentially the same dose-response curve. If the effects of the two compounds when given together were merely additive, then the initial dose of phenolphthalein plus the initial dose of cascara sagrada should produce the same effect as a double dose of either compound alone. It is readily apparent, however, that the action of the laxative compound tablets cannot be explained merely on the basis of the additive effects of cascara sagrada and phenolphthalein. This study indicates that the potentiated action of ingredients in the laxative compound tablets results in a qualitatively different type of laxative action quite distinct from that of phenolphthalein or cascara sagrada alone. To date this laxative compound tablet is the only preparation known to have this type of action.

SUMMARY

1. A controlled and balanced "blind-test" has been conducted in 50 elderly constipated patients to study the laxative action of cascara sagrada, phenolphthalein, and laxative compound tablets.

2. The laxative compound tablets had an action greater than the additive effects of its ingredients.

3. The laxative compound tablets produced a qualitatively distinct type of action, characterized by stools of soft consistency with a minimum of hard or

watery stools. On the basis of statistics, this pattern of action was significantly different from that of phenolphthalein and cascara sagrada in the dosage used.

4. The number of stools was increased from about 0.2 to 1.0 per day by the laxative compound tablet.

5. The laxative compound tablets had a significant "tonic" effect. While taking them, patients experienced an increase in the sense of well-being. It was not determined whether this tonic effect was related to the laxative effect or to some other mechanism.

6. The favorable effects observed from laxative compound tablets would seem to make them particularly suited for use by the chronically constipated patient, especially the elderly, and by those postoperative patients in whom soft stools are particularly desirable.

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CARCINOMA OF THE COLON AND RECTUM IN GERIATRICS

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The rapidly progressing specialty of geriatrics is changing our concept of the treatment of carcinoma of the rectum and colon. Not too long ago, the individual of 65 or 70 years of age was considered "too old to stand an operation." Now we have come to realize that age, alone, is no barrier to radical surgery. Patients in the upper decades tolerate surgery as well as younger individuals, provided, of course, that our evaluation of their physiologic age is correct and our preoperative and postoperative treatment individualized accordingly. The chronologic age can be disregarded.

Older patients are being submitted to major resections. The trend can be graphically illustrated by comparison of the average age of 100 consecutive patients who underwent an operation for carcinoma of the rectum and sigmoid prior to 1941, with the average age in a similar series in which the operation was performed since 1951. Table 1 shows the average age in the group most recently operated on to be increased by five years.

The table also shows a change in the type of surgical procedure. Since 1951 fewer palliative operations were performed, as shown by the reduction in the number of colostomies, with a corresponding increase in the number of major resections. Although there was a decrease in the number of abdomino-perineal resections, the number of anastamoses increased from 6 per cent to 47 per cent. It is to be noted that, in spite of more extensive surgery in an older age group, there was no corresponding increase in mortality. In fact, there was a definite reduction in operative mortality—from 8 per cent to 2 per cent. This we feel to be due to two main factors: 1) antibiotics reducing infection, and 2) the judicious use of whole blood and fluids, both preoperatively and postoperatively.

Antibiotics are very important in maintaining low mortality in all cases of colon surgery. However, in the geriatric patient, we feel minute attention to physiology is a vital factor. The possibility of physiologic changes in addition to the carcinomatous changes increases with age, so that the older the patient, the greater the evaluation of incipient or apparent disease should be.

The geriatric candidate for radical surgery affords an excellent opportunity for the demonstration of cooperation between the geriatrician and the surgeon. It is important to evaluate adequately the cardiac, nutritional and general physiologic level, prior to surgery. Patients should be hospitalized for several days before surgery is contemplated, in order to study these variables, for many will show hypoproteinemia, hypochloremia, anemia, and mild degrees of cardiac decompensation. These should be corrected and the patients made as near normal as possible prior to elective surgery. If they are very poor operative risks,

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particularly from a cardiac or senescent standpoint, the operative procedure should be scaled or selected to furnish the longest palliation with the least surgical risk. Many of their so-called senile changes will disappear with adequate preoperative correction of anemia, hypovitaminosis, hypoproteinemia and hypochloremia. Practically all of these patients, unless moribund, can be either operated on and cured of their disease, or relieved temporarily. Palliation may permit them to live out their remaining life-spans in comfort until they succumb to some other disease process.

The diagnostic procedures for carcinoma are well established, but the importance of blood in the stool should be emphasized. This should be assumed to be from carcinoma until proven otherwise, particularly in the older age group. Hemorrhoids should be accused only after thorough search for carcinoma of the rectum and colon has been fruitless. Digital examination of the anus and rectum will lead to the diagnosis in 60 per cent of all carcinomas; sigmoidoscopic exami-

TABLE 1

Surgical procedure	100 Cases since 1951			100 Cases prior to 1941		
	No. of patients	Avge. age	Deaths* postop.	No. of patients	Avge. age	Deaths* postop.
Abdomino-perineal resection	32	62½		46	52½	6
Anastomosis	47	63¼		6	57	
Posterior resection	7	76		5	63	1
Palliative colostomy	5	64	2	20	66½	1
Coagulation	9	65½		23	61¼	
Total	*100*	*63¼*	*2*	*100*	*58½*	*8*

* All deaths within one month following surgery.

nation will give similar results in 80 to 90 per cent of all carcinomas of the large intestine. The most important thing for the sigmoidoscopist to search for is evidence of blood or blood-streaked mucus high in the rectal ampulla or in the sigmoid. If no lesion can be found in the area the sigmoidoscope reaches, and blood or blood-stained mucus is present, the patient should undergo x-ray examination for evidence of a higher lesion. Blood or blood-streaked mucus at the rectosigmoid junction or higher, is pathognomonic of a lesion above this level. Diverticulae are a frequent x-ray finding in this age group, but since they so rarely are the source of intermittent bleeding, the burden of proof rests with the roentgenologist that no other pathologic condition is present. Only by examination in this manner will early lesions be found that can be totally removed and the patient cured. Sigmoidoscopic examination is the only means of diagnosing lesions high in the rectum and in the lower sigmoid, for x-ray examination in this area is entirely inadequate. The roentgenologist should be one trained in examining the colon and have the ability to recognize small lesions. This usually means double enemas with thin and thick barium, and each with

air contrast. Every inch of the colon that can be palpated should be examined fluoroscopically under pressure.

Surgical principles are the same for all age groups. When the geriatric patient cannot be rehabilitated sufficiently to withstand major procedures, minimal surgery or local palliative measures may be used. Fulguration of a low rectal neoplasm is a satisfactory palliative procedure.

The prognosis in surgical excision of carcinoma of the rectum and colon may be favored by certain phases of the aging process. Diminishing lymphatic circulation discourages early metastases; even with adjacent lymph gland involvement, the possibility of distant metastases is less. The rate of growth of a neoplasm is also slower in the elderly patient with less active circulation. Even when the primary growth is removed as a palliative measure only, the period of palliation may be a comparatively long one.

Early ambulation is of more importance to the elderly patient than to the younger, but should be undertaken in moderation. There is some degree of arteriosclerotic change in all geriatric patients, and a greater tendency for thromboembolic disease. Getting these patients up for even a very short time on the first or second postoperative day improves their circulation, their mental reactions, and helps to prevent thrombosis or embolism.

Fluid and electrolyte therapy (1, 2) should be instituted quite early postoperatively, for aged patients withstand changes poorly. The resistance of plasma volume to dehydration is not as prolonged as in younger patients. The loss of fluid and electrolytes by way of the urine, by gastric suction (if used), by vomiting, and by insensible perspiration, should be estimated daily and the amount restored to the body. The efficacy of fluid and electrolyte therapy is greatly enhanced by blood transfusion; one should not wait for clinical shock in the aged, but should administer blood as prophylaxis. Frequent small transfusions are very helpful. The hallucinations and delirium found in the geriatric patient postoperatively are frequently due to electrolyte imbalance, and respond dramatically to administration of the correct solution. Intravenous sodium chloride solution is frequently all that is required. Fluids should be given slowly, intravenously or subcutaneously, to the patient with hypertensive cardiovascular disease.

SUMMARY

1. Physiologic age and not chronologic age is a deciding factor in determining whether a patient should be submitted to major surgery of the colon or rectum.

2. A series of 100 consecutive major operative procedures on the colon and rectum performed before 1941, and since 1951, are compared. This series shows that it is possible to perform major surgery of the colon and rectum in an older age group (an average of five years older) with a definitely lowered operative mortality. This is due to the use of antibiotics and to physiologic control of fluid and electrolytes in the preoperative and postoperative periods.

3. The importance of cooperation between geriatrician and surgeon in the preoperative and postoperative periods is emphasized. All physiologic variables,

particularly fluid and electrolytes, should be adjusted and maintained at as near a normal level as possible.

4. The diagnostic significance of blood in the stool is emphasized, and the proper methods for determining its source are outlined.

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THE EARLY DIAGNOSIS OF BOWEL OBSTRUCTION

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To the general practitioner, and also to the surgeon, the problem of intestinal obstruction is often difficult, because of the many different forms in which it occurs and because, early in the disease, the symptoms may not be very severe. For example, there may be a complete absence of, or relatively little tenderness in the abdomen, and no fever—symptoms usually present in other forms of acute surgical conditions in the abdomen. This leads to delay in diagnosis and treatment. Early diagnosis is of paramount importance in this often fatal disease. It must be recognized that the condition carries with it its own toxemia, which will prostrate the patient without much delay and which will often kill, even when the exciting cause has been corrected.

The subject matter in this discussion will be limited to acute mechanical intestinal obstruction. It will not include the obstructions of nervous or circulatory origin such as paralytic ileus (which occurs as part of the peritonitis syndrome or in reflex shock), the more rare spastic types of occlusion, or mesenteric thrombosis and embolism.

CLASSIFICATION

Etiologically there are many varieties of mechanical obstruction, and there have been many attempts to classify them. Wangensteen's (1) description is outstanding. These classifications are especially valuable for the purpose of completeness and teaching; but to simplify the subject a better perspective is needed of the more common causes, with their relative frequency. In going over a series of 200 consecutive cases of acute mechanical obstruction at the Cook County Hospital (2), it was found that they could be divided into five groups, with the rates of incidence, as follows:

A. Herniae	33%
B. Bands and adhesions	22%
C. Inflammatory lesions	20%
D. Carcinoma	18%
E. Miscellaneous—intussusception, volvulus, tumors, atresias, congenital defects, foreign bodies, etc.	7%

No claim is made that these averages will be universally correct in a larger series of cases; moreover, in this series of cases children were not included. Had they been, the relative incidence, especially in group E, would undoubtedly have been higher. However, it will be seen that the vast majority of bowel obstructions belong in the first four categories.

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Therefore, one thinks of these four categories first, when confronted with a patient with the cardinal symptoms of bowel obstruction, namely: 1) crampy abdominal pain, 2) vomiting, 3) distention, and 4) obstipation.

A. *Hernia*

This is usually obvious as a visible, sometimes tender mass at one of the common hernial sites. Small masses, seen especially in the femoral region (so-called Littre hernia) with only a portion of the bowel lumen involved, are not so easily diagnosed. Internal hernias and diaphragmatic hernias are sometimes complicated by strangulated gut and need to be kept in mind in going through the usual diagnostic procedures. The mere presence of a hernial mass does not necessarily mean that the obstruction is in the hernia. Distention of the bowel from obstruction elsewhere may cause the bowel to bulge into a previous hernial sac and give the appearance of a strangulated hernia. To obviate this error the hernia is reduced if possible, and the patient observed for further evidence of obstruction.

B. *Bands and adhesions*

These may be suspected as the cause of the obstruction if abdominal scars are present or if there is a history of previous peritonitis. Two types of obstruction occur in this connection: 1) simple obstruction by a bolus of food; in this case there should be a history of bulky food intake, and relatively little tenderness locally, and 2) strangulation of the gut by a band; in this case the symptoms become rapidly severe with varying amounts of local tenderness, usually near the scar, and with developing signs of peritoneal irritation. The problem is to differentiate between simple food obstruction and strangulation. This is not always easy. Strangulation demands early recognition and early surgery, whereas simple obstruction by a bolus of food is generally better treated conservatively.

C. *Inflammatory lesions*

This type of obstruction comes about because one or more loops of bowel become involved in the walling off of an inflammatory process in the abdomen or pelvis; for example, the loops of edematous and occluded bowel which, with the omentum, serve to localize an appendiceal mass or abscess. In this instance there should be a history of an acute inflammatory process preceding obstructive symptoms. Palpation may reveal a tender mass, and the presence of fever should make one suspicious of an inflammatory cause. In any bowel obstruction the presence of fever must be explained and not be taken for granted. Obstruction caused by an inflammatory lesion carries with it a high mortality if operated upon inadvertently or without considerable circumspection, even in this day of antibiotics. In the majority of these cases the obstruction is due to edema and simple occlusion of the bowel, and the patients respond well to conservative management.

D. *Carcinoma*

In patients over 40 years of age with symptoms of bowel obstruction, with no hernial mass, fever, or scar of previous surgery, carcinoma should be suspected;

more so, if there is also a history of weight loss, change of bowel habits, or blood in the stools. Nearly all carcinomas are found in the colon, most of them in the left colon, many of them in the rectum and the recto-sigmoid flexure where they can be felt by the examining finger in the rectum and diagnosed immediately.

E. *Miscellaneous*

The less common mechanical obstructions must be considered individually. Volvulus and foreign bodies can usually be seen in the flat x-ray plate of the abdomen. Intussusception and congenital defects usually occur in children, but must be borne in mind in adults as well.

In making a diagnosis of acute mechanical obstruction of the bowel it is necessary to establish: 1. The fact that the bowel is obstructed. 2. The nature and location of the obstruction. 3. Whether the blood supply to the bowel is compromised by strangulation or pressure.

Frequently lost sight of is the matter of circulation of fluids in the bowel. These fluids are made in large quantities (two quarts or more per day) in the mouth, the stomach, the biliary and pancreatic tracts, and the upper reaches of the small bowel for purposes of digestion, and to keep the contents of the small bowel normally liquid. These fluids are re-absorbed in the colon. It is the blocking of these liquids that produces the symptoms of persistent vomiting, the distention, the borborygmi, the dehydration and loss of electrolytes, and may contribute to the toxemia which is peculiar to intestinal obstruction.

DIAGNOSIS

History

Skill in getting a good history is still the most valuable procedure in diagnosis. Exactly how and when the symptoms occurred, the character and frequency of pains, vomiting and bowel movements, the food intake, and the preceding history should be recorded and carefully considered before a diagnosis is made. A good history is half the diagnosis and it should never be made in haphazard fashion, in the hope that x-ray examination or other laboratory procedures will provide all the required information.

Physical examination

A routine general examination is then made and the results recorded, including temperature, pulse and respiration.

Inspection. The entire abdomen is examined carefully for hernial masses, scars of previous surgery, evidence of weight loss and evidence of distention. The ordinary medium-weight or thin individual lying on his back, will present a concavity of the abdomen to a line drawn from the ensiform cartilage to the pubes; absence of this concavity in these subjects suggests beginning distention. Further evidence of progressive distention can be made by simply measuring the girth at the umbilicus with a tape measure from time to time. Visible peristalsis is evidence of chronic or partial obstruction, not of acute obstruction.

Palpation of the abdomen, together with rectal and vaginal examinations, may be quite revealing in finding masses and tender areas; the complete absence of

tenderness does not rule out bowel obstruction. The relatively slight tenderness found when a bolus of food obstructs the bowel, compared with the relatively greater tenderness found when the bowel becomes strangulated, serves to differentiate between the two conditions. A tender mass, especially if the patient has a fever, should raise the question of inflammation and call for a more careful consideration of the history.

Auscultation of the abdomen. This is a procedure which is not used frequently enough, yet it is one of the most reliable of diagnostic measures. The presence of borborygmic rushes (also known as obstructive peristalsis) is characteristic and, to the experienced ear, almost pathognomonic. These rushes occur synchronously with the crampy pains, thereby fixing the bowel as the origin of the pain. They not only help in making an early diagnosis, but are a source of constant information in observing the progress of conditions within the abdomen. The rapid accumulation of fluid and gases in the area proximal to the obstruction, produces these characteristic sounds with each wave of peristalsis. Early, these sounds are low pitched and frequent, but as time goes on and the proximal bowel becomes more and more distended, they become higher in pitch, and farther apart, until with the complete ballooning out of the abdomen, peristalsis finally ceases and only an occasional tinkle can be heard after listening for long periods of time. The presence of active peristaltic sounds differentiates mechanical ileus from paralytic ileus. In other words, if one hears active peristalsis in the abdomen, one need not be concerned about peritonitis. When strangulation of the bowel occurs and the peritoneal cavity becomes wet with extravasated fluid and blood, there is also a marked quieting down of the peristaltic sounds characteristic of peritoneal irritation.

Symptoms

Character of pain. Pain, in mechanical obstruction, is of a crampy nature. Like the initial pain in acute appendicitis, which is also a peristaltic pain, it is typically located vaguely in the midepigastric area, regardless of the location of the lesion. Localization comes only when complicated by strangulation or inflammation. Tenderness may be entirely absent. When pain occurs at the time of the peristaltic rush, it aids in relating the pain to the bowel. It is usually rather sudden in onset, and its relative violence also serves to differentiate to some extent between simple obstruction and strangulation. When the bowel becomes strangulated, a residual pain with a superimposed crampy pain becomes evident, again serving to differentiate between simple obstruction and strangulation. This type of pain may also be present in the inflammatory lesions.

Character of vomiting. At the onset of the obstruction, because of the insult to the bowel, vomiting is common; but it is not the vomiting characteristic of obstruction. When this begins it is the regurgitation due to reversed peristalsis. Large amounts of fluid back up into the stomach to be vomited, unless removed by a Levine tube with suction. Once started, this vomiting is continuous; first the stomach contents, then material from the upper reaches of small bowel, then feculent material from the ileum. To some extent the frequency of vomiting

and the rapidity with which it takes place will give a clue to the location of the lesion. Early, frequent vomiting is characteristic of small-bowel obstruction, whereas colon obstruction may be present for days (with even marked distention of the proximal section) before vomiting begins—depending, of course, on the patency of the ileocecal valve.

Bowel movements. The bowel distal to the lesion tends to empty itself within twelve to twenty-four hours from the onset of the obstruction. True obstipation then supervenes. Any passage of feces or gas after this, rules against true obstruction.

X-ray examination

A flat plate (Scout picture), or examination under the fluoroscope, is always a valuable help in an acute abdominal condition. In bowel obstruction one should not wait for the characteristic herringbone pattern or layers of gas and fluids to appear. One or two loops of small bowel containing bubbles of gas not normally seen there, or an obviously distended loop or two, is fairly good evidence of obstruction. Outlines of a distended colon proximal to the colonic lesion can often be seen. Volvulus produces a characteristic picture of a markedly distended loop of colon arising usually from the sigmoid region. Barium enemas are helpful in diagnosing the colonic lesion with regard to its nature and location; barium should never be given by mouth, however, when bowel obstruction is suspected. Foreign bodies may sometimes be seen, such as a gall stone lodged in the region of the ileocecal valve.

Preliminary treatment

Mineral oil and enema routine. Most patients on entering the hospital need a period of observation and preparation for surgery, if and when surgery is needed. During this period, when the patient is being deflated with one of the several tubes and his fluid and electrolyte balance is being restored, it is the custom at the Cook County Hospital to start what we call "the mineral oil and enema routine." The patient gets 2 ounces of mineral oil by mouth every four hours, closing off the Levine tube for a half-hour period after each dose; a two-quart soapsuds enema is given every four hours (using lubricating jelly on the rectal tube, not vaseline or oil). Presence of oil in the enema return means either: a) there is no obstruction, b) if obstruction is present, it is only partial, or c) the obstruction has been relieved. This procedure is especially valuable in the relief of simple obstructions. If they are relieved, or if there is no real obstruction, the oil usually appears within about twelve hours. It should also be noted how much of the two-quart enema the patient can retain, as an aid in determining whether the colon is involved.

SUMMARY

An attempt has been made to simplify the problem of bowel obstruction and to emphasize the more common varieties. Every medical student remembers the ominous words intussusception, volvulus, and congenital atresia. These

conditions and others relatively as rare will most likely come to mind when he is confronted with a case of bowel obstruction. A better perspective is needed of this broad field. Some of the more useful diagnostic features as practiced daily at the Cook County Hospital are described.

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EFFECTIVENESS OF RADIOTHERAPY IN CANCER OF THE UTERINE CERVIX*

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Almost half of all patients with cancer of the cervix can now be cured by radiotherapy if the best available techniques are used. An even larger proportion may be salvaged if recent promising developments are applied.

Ever since the first long-term results in radiotherapy of cervical cancer were published, there has been a progressive improvement. For example, at the Radiumhemmet, Stockholm, in the course of thirty years, the overall five-year cure rate has risen from about 20 per cent up to 45 per cent. Numerous clinics now report a salvage rate of more than 40 per cent and an occasional one reports absolute figures that just exceed 50 per cent. However, the majority of centers still do not attain a cure rate of 40 per cent (1).

Although some clinics owe their improved overall result to more favorable clinical material, others, such as the one in Stockholm, have no greater proportion of early cases of the disease. Their superior cure rate can only be explained on the basis of better radiotherapy. This is particularly evident in Stage II and III (International classification), as may be seen in Table 1. Their advantage stems partly from the concentration of a large amount of clinical material in capable hands. About 300 new cases of cervical cancer are seen there each year. Since 1910, there have been only three men in charge of the gynecologic cancers—Forssell, the founder; Heyman, the chief from 1915 to 1947; and Kottmeier, the present chief. The latter two have devoted their entire time to gynecologic radiotherapy. This is a particular advantage because of the empirical nature of radiotherapy. It has been developed by applying a given amount of radiation and carefully observing over weeks and years what has happened. If the result is good, that technique is used again; if unsatisfactory, it is abandoned for some other method. Thus the evolution of an effective technique is favored by careful personal observation of a large number of cases over a long period of time.

It is, of course, impossible to define the characteristics of superior radiotherapy, but two aspects of this problem should be stressed.

General condition of the patient. First, the importance of the general condition of the patient should not be underestimated. Because radiotherapy is rather easily and painlessly applied, it is sometimes given to ambulatory patients with little

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Schering Corporation supplied testosterone propionate, and Abbott Laboratories supplied the alpha-tocopherol.

consideration of their general condition. On the other hand, no one would think of radical surgery in that same patient without careful preoperative and postoperative attention to nutritional status, hemoglobin, local infection, and rest during treatment and convalescence. These same considerations are as important to the radiotherapy patient as to the surgical patient. The superior results attained in some clinics are at least partly explained in this manner. McKelvey (2) hospitalizes his patients during the entire treatment, which seems expensive; but it is obviously well worthwhile, as indicated by his over-all cure rate of 54 per cent. Hospitalization assures close surveillance by the staff, an adequate diet, and the rest that is usually impossible to achieve at home in the face of cooking, laundering and housekeeping demands.

It is difficult to say precisely how much importance to attach to the general care of the patient, because the clinics that pay the most attention to it are the clinics in which radiotherapy is superior in other respects. An index, however, of its importance may be seen in the influence of fever on the course of therapy. At the Marie Curie Hospital in London, among 568 patients with no fever during therapy, 52 per cent were cured (five years), whereas only 14 per cent of the 286

TABLE I

Five-Year Cure Rate in Cervical Cancer Patients Treated Radiologically During the Years 1941 to 1945 (1)

	Total No. Cases	Cure Rate (%)				
		All Stages	Stage I	Stage II	Stage III	Stage IV
Stockholm	1473	44	69	51	27	13
Boston	322	38	68	43	15	9

patients who had a temperature of 101° or more, during or immediately following treatment, were cured (3). Comparable results are found in a recent series in Stockholm (4).

Dosage. The second facet of this problem is the fundamental principle involved in radiation treatment of cancer. Is it simply a question of giving a large enough dose to kill the cancer, or is a more subtle element involved? Radiotherapy has been used for more than half a century and yet we do not know how it "cures" the cancer. Undoubtedly, it damages the tumor by its direct effect, but this cannot entirely explain the control. Experiments show that radiation of the site where untreated tumor is subsequently transplanted will prevent the survival of the transplant, whereas similar exposure of the tumor itself will not keep it from surviving and growing if it is promptly transplanted to a nonirradiated area (5). In like fashion, radiation of the tissue surrounding a tumor may cause it to regress, even though the tumor itself is not touched by the ionizing rays (6). These experiments indicate that factors other than the direct damaging effect must be at work in the "cure" of cancer.

Before the first World War, Forssell and others recognized the importance of this factor. They called it the *healing process*, which refers to the local inflam-

matory response as well as the patient's general resistance to the tumor, a process that is analogous to the local and general resistance elicited by a bacterial infection. Modest doses of ionizing radiation enhance and help this process, whereas large doses of radiation over a wide area discourage and may destroy the healing process and thus actually result in fewer cures (4, 7). This philosophy guides the therapy at the Radiumhemmet, where regard for the healing process restricts the dose administered to the node-bearing areas to no more than 2500 r from x-ray, in addition to the 1200 r_γ from the radium in a period of nine weeks. It is recognized that the primary tumor in the cervix must receive a substantial dose (7000 mg. hrs. in three weeks) but larger doses of x-ray have been found to be detrimental. The results in clinics using this technique are unexcelled.

Prognosis. Even the best radiotherapy at present fails in half of the patients. If one must wait until a recurrence is grossly evident to determine the effectiveness of treatment, the chance of saving that patient is almost nil. On the other hand, recognition that the treatment has been ineffective during or immediately after treatment would allow other, possibly more effective measures to be taken.

This problem has been well known for many years and a number of possible solutions tried. The gross appearance of the tumor during radiotherapy is a poor guide, in that one tumor that melts rapidly away under treatment may recur within a few months, whereas another tumor that only slowly disappears and leaves much firm induration may actually be cured.

Because the clinical findings are so unreliable, there has been a shift to microscopic examination, in the hope that it would be more productive. The histologic appearance of the tumor prior to treatment has been thoroughly studied, all to no avail. Of two patients with the same type and histologic grade of tumor and the same clinical extent of disease, treated alike, one may succumb and one survive. The grading of the tumor has no practical importance as far as prognosis of cervical cancer treated by radiation is concerned (8).

However, Glucksmann of Cambridge, England, has developed a method of *histologic prognosis* during treatment that is effective (9). Serial biopsies are performed after each radium treatment. He requires a growing edge of tumor for his examination. Differential counts are made on tumor cells in the sectioned material and the number of degenerating and differentiating cancer cells are plotted against the number of resting cancer cells and those in mitosis. A significant increase in degenerating and differentiating cells indicates a favorable response to the radiation. His accuracy of prognosis by this method in a large series of cases is 87 per cent. The method has the disadvantage that it requires multiple large biopsy specimens which become difficult to obtain as treatment progresses. Because of this, Glucksmann was not able to make a prognosis in 24 per cent of the Stage I cases in his series.

In the Vincent Memorial Laboratory, R. M. Graham has developed a method of prognosis based on the amount of radiation change seen in the benign squamous epithelial cells of the vaginal smear during radiation treatment—*the cytologic response*. During radiotherapy, all cervical cancer patients show some radiation effect in the nonmalignant epithelial cells of the vaginal smear. It is manifested

by vacuolization of the cytoplasm, increase in cell size, multiple nuclei and nuclear alterations. If less than 60 per cent of the cells show these changes, the outlook is bad and the response is called "poor." However, if 75 per cent or more of the cells show these changes, the prognosis is comparatively good and the response is called "good." In a series of 125 patients at the Vincent Memorial-Massachusetts General Hospitals, 62 had a "good response" and of these, 59 per cent were living and well at five years; 63 had a "poor response" and only 3 per cent lived five years (10).

This observation has been confirmed in Copenhagen by Anna Margarethe Nielsen in a similar series of 100 cases. In this series 73 patients with "good"

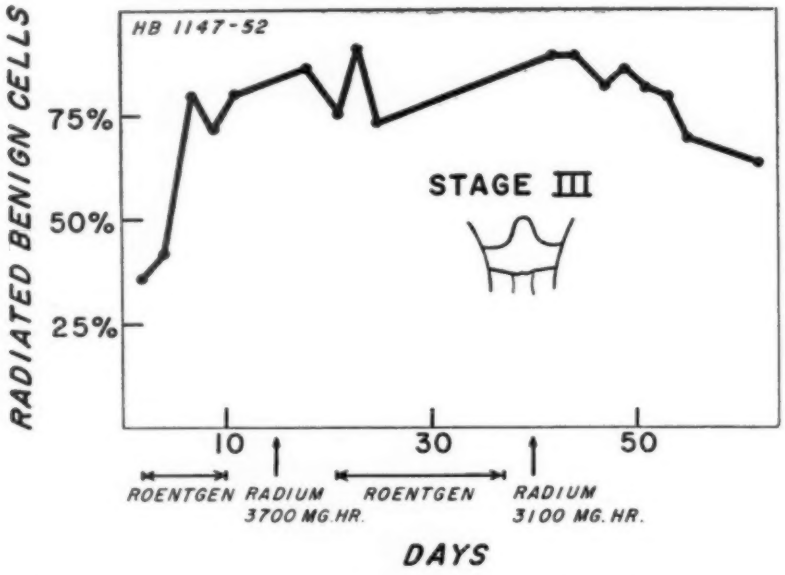

FIG. 1. Good cytologic response, spontaneous. HB 1147-52—Radiumhemmet, age 62 para IV, stage III. Nov. 4 to Nov. 11, 1952. Roentgen rays, perineal, 2000 r. Dec. 9, 1952. Radium, 1430 mg. hrs. in uterus, 2250 mg. hrs. in vagina. Dec. 15 to Dec. 31, 1952. Roentgen rays, 2400 r, two anterior ports, sparing midline. Jan. 3, 1953. Radium, 1350 mg. hrs. in uterus, 1800 mg. hrs. in vagina. Feb. 2 to Feb. 12, 1953. Roentgen rays, 1600 r, two posterior ports, sparing midline.

responses showed only 6 per cent recurrences, whereas among 27 patients with poor cytologic responses, 21 (74 per cent) showed a recurrence in the course of twelve to thirty-two months (11).

A good cytologic response is shown in Figure 1. This patient was aged 61, a para IV with a Stage III carcinoma of the cervix extending out to both pelvic walls (where it was firmly fixed) and down the posterior vaginal wall almost to the introitus. She was treated with x-ray and radium. The benign cells showing radiation effect rapidly rose above 75 per cent and ultimately reached 92 per cent. Her prognosis is regarded as good.

A poor cytologic response is shown in Figure 2. This patient was aged 55, a para II who had an endocervical Stage II lesion with some fibrotic attachment

to the pelvic wall. She was given two applications of radium and later received x-ray. Her percentage of nonmalignant cells showing radiation effect never exceeded 57 per cent. Her outlook is poor.

This method of prognosis has now been perfected so that it is possible to distinguish the good and the poor response after a single radium application, when two radium applications are the definitive treatment, or after only 1000 r (tumor dose) of x-ray (12).

Effective prognosis based on changes in the nonmalignant cells implies that the patient's susceptibility to radiation is of some importance. If this is so, alteration of the individual's sensitivity to radiation might be of value in the resistant case.

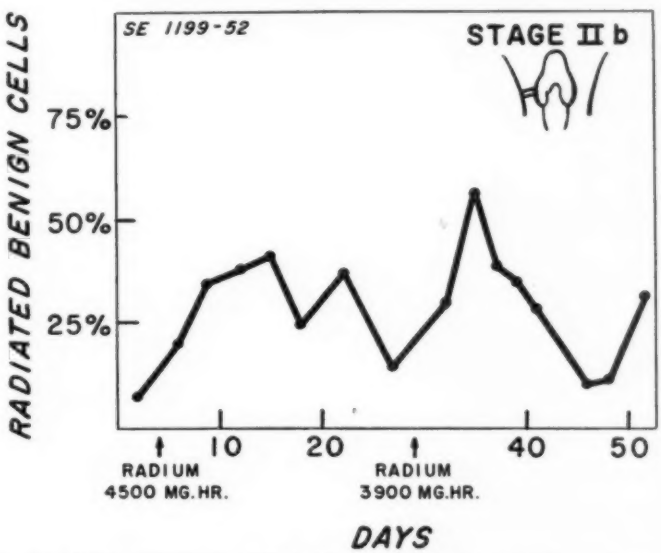

FIG. 2. Poor cytologic response. SE 1199-52—Radiumhemmet, age 55, para II, stage IIb, endocervical. Dec. 11, 1952. Radium, 3500 mg. hrs. in uterine and cervical canal. Jan. 3, 1953. 2000 mg. hrs. in uterine canal, 1900 mg. hrs. in vagina. Roentgen ray therapy, sparing the midline, was given at another hospital beginning three weeks later.

The administration of certain substances, *e.g.*, testosterone propionate or alpha-tocopherol, has been found to make animals abnormally sensitive to total body radiation, as indicated by an increased death rate (13). Accordingly, a cervical cancer patient was observed during the early phase of her radiotherapy and recognized as a "poor response." She was then started on testosterone propionate, 25 mg. three times a week intramuscularly, which was continued during the remainder of her radiotherapy. The proportion of her vaginal-smear cells showing radiation effect rose sharply to a level found only in a "good response." This experience with *supplemental therapy* was confirmed in 6 additional cases. In 3, alpha-tocopherol (100 mg. daily by mouth) was used instead of the testosterone, with the same apparent beneficial effect. Of the 7 with an initial "poor response," 6 changed to a "good response." The patient who could not be changed cytologically died rather promptly. Of the remaining 6, 1 is dead, 1 has a recur-

rence, and 4 are living and well at present, one to two years later (12). Since then a series of 100 consecutive cases has been similarly studied and given supplemental therapy at the Radiumhemmet, Stockholm. The immediate results are essentially the same as those in the pilot series.

An initially poor cytologic response is shown in Figure 3 in a patient, aged 41, para III, with a Stage III lesion fixed to the left pelvic wall. After a rather heavy dose of 4800 mg. hrs. of radium, the radiation-effect cells rose no higher than 34 per cent. Therefore, after her second radium treatment alpha-tocopherol, 100 mg. a day, was started and continued during the remainder of her radiotherapy. Her cells showing radiation effect rose to 85 per cent, a level regarded

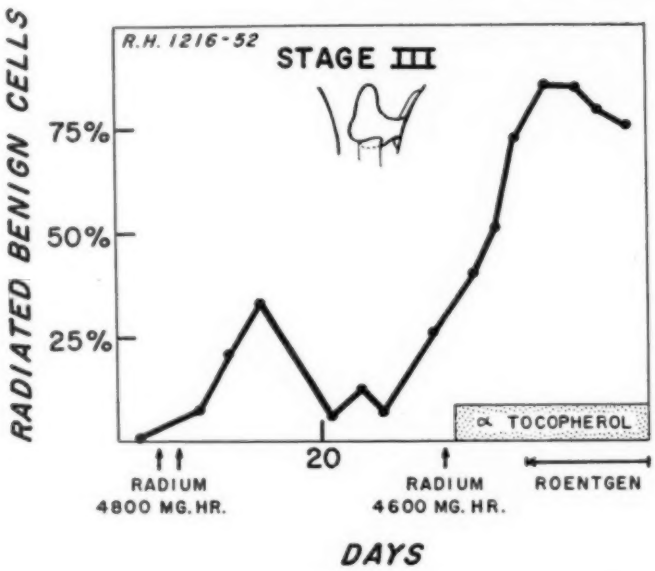

FIG. 3. Poor initial cytologic response changed to good cytologic response. RH 1216-52—Radiumhemmet, age 41, para III, stage III. Dec. 16, 1952. Radium, 25000 mg. hrs. in uterus. Dec. 18, 1952. 2300 mg. hrs. in vagina. Jan. 13, 1953. 2200 mg. hrs. in uterus, 2400 mg. hrs. in vagina. Jan. 14, 1953. Began alpha-tocopherol, 100 mg./day, orally. Jan. 21, 1953. Began roentgen ray therapy, 2400 r, sparing the midline.

as good. It is quite certain that such a favorable response would not occur after such a poor initial response without supplementary therapy. Whether her clinical course will parallel the improvement in her cytologic response remains to be seen.

Recently we have found that there are characteristic changes in the benign epithelial vaginal cells *prior* to treatment which, if present, presage a good chance of cure. If these changes are absent before treatment, the outlook is poor in all except the very early case. The changes are found in the "basal" cells and consist of fine vacuolization and an increased density of the cytoplasm. They are referred to as the *sensitization response*, or SR. If 10 per cent or more of the benign epithelial cells show these changes, SR is called good; if 9 per cent or less, SR is called poor. In 100 patients treated radiologically, 35 had good SR,

and of these, 66 per cent were living and well at five years; of the 65 with poor SR, only 18 per cent survived five years. Seventy per cent of 20 Stage II patients with good SR were cured, whereas only 28 per cent of 25 Stage II patients with poor SR survived. Five out of 8 Stage III patients with good SR were cured, but only 1 of the 21 Stage III patients with poor SR survived (14).

It may be noted in Figure 1 that the incidence of cells showing radiation effect does not start from zero, but rather from 37 per cent, which in reality is the SR. The cellular picture of SR is similar to that following early radiation and was originally confused with the radiation effect. The patient in Figure 1 had a good SR and showed a favorable response cytologically to radiation. By contrast, Figure 2 begins at 7 per cent, denoting that level of SR before therapy; and this patient failed to show a satisfactory cytologic response during her treatment. Thus her outlook is bad by both criteria. In Figure 3 the patient had no SR and her initial response to radium was poor. It was only after supplementary therapy that the level of cells showing radiation effect attained a satisfactory peak.

We interpret the SR as a manifestation of resistance, a reaction of the host elicited by the tumor. When this resistance is present, the tumor is at least partially held in check. Radiotherapy given under these circumstances, when the forces of the body are already mobilized, may be expected to eradicate the tumor. However, in the more advanced case the resistance to the tumor may be finally exhausted. SR, previously present, may disappear and radiotherapy given under these circumstances temporarily damages the tumor, but is quite incapable of controlling the disease.

Recognition of the patient with poor SR before treatment would appear to offer some advantage. If she is to be treated radiologically, a period can be spent in an effort to improve her SR, with the reasonable expectation of making her radiotherapy more effective. The SR may increase while the patient rests in the hospital prior to therapy. For example: a patient with a Stage II lesion was found to have 12 per cent SR on the day of admission. During her weeks' stay on the ward she received a high-protein diet and was studied carefully. By the end of the week, her SR had risen from 12 per cent up to 54 per cent. She showed a favorable clinical and cytologic response during treatment and is well at present, almost three years later. The same supplemental therapy (testosterone propionate or tocopherol) that will improve the cytologic response during radiotherapy will also improve SR before the patient is radiated.

With these observations in mind, the following program is suggested.

Program for radiation therapy in cancer of the cervix

The patient is admitted for at least a week prior to treatment. During this period she is ambulatory but confined to the ward. She is thoroughly studied and receives a high-protein, high-vitamin diet. Her anemia, if any, is corrected. Other defects, *e.g.*, diabetes, or cardiac disease, are dealt with. Local infection is counteracted by local hygiene and generally applied antibiotics. Daily vaginal smears show whether the sensitization response (SR) is present in sufficient amount. If it is not, supplemental therapy in the form of testosterone propio-

nate (25 mg. three times a week) or alpha-tocopherol (100 mg. per day, orally) is given during the course of radiotherapy. The patient is kept in the hospital during her entire course of treatment. If the desired changes in the vaginal smear during therapy do not occur, radiotherapy should be abandoned and the patient subjected to radical surgery.

SUMMARY

Attention to and improvement of the general condition of the patient, along with an avoidance of excessive amounts of radiation, will advance the results of radiotherapy in cancer of the uterine cervix.

A prognosis of whether or not the radiotherapy is likely to be effective can now be made by noting changes in the nonmalignant cells of the vaginal smear. This recognition is possible not only at the end of the treatment, but midway in therapy and, even more important, before treatment is begun. Recent experimental work in patients, calculated to enhance the effectiveness of radiotherapy by giving modest doses of testosterone propionate or alpha-tocopherol, is described.

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PROLAPSE OF THE UTERUS

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Prolapse of the uterus is most common above 40 years of age. It is the primary diagnosis in 4.5 per cent of gynecologic diagnoses at Temple University Hospital. In our experience it is an anatomic defect, largely of white women. There is no explanation for the almost negligible incidence of carcinoma of the cervix in women with prolapse (Fig. 1).

ETIOLOGY

There seems to be no doubt that the uterus and upper third of the vagina are supported by a condensation of endopelvic fascia. This condensation is made up of fibrous tissue that forms the uterosacral ligaments and the parametrium. The fusion or condensation, is often referred to as the cardinal ligament or transverse cervical ligament of Mackenrodt.

Trauma during childbirth is undoubtedly the chief cause of prolapse; however every physician of experience has seen complete prolapse through an unruptured hymen. In such cases we find (at surgery) practically no substance to the transverse cervical ligaments. In the average case, both of these factors (childbirth injury and congenital attenuation) may play etiologic roles. One might well speculate that if obstetrics as practiced since 1930 is favorably disposing the internal genitalia to good health, the incidence of prolapse should gradually decrease to zero, except for the congenital variety. In the future the incidence of prolapse should be further reduced by the earlier correction of cystourethroceles, since the transverse cervical ligaments are used in such repairs.

PATHOLOGY

When the cervix descends over the perineum and beyond, this condition is referred to as second and third degree prolapse. At this time it will be noted that certain pathologic changes are starting to take place. The cervix itself becomes enlarged and edematous. Hypertrophy takes place mainly in regard to length, so that the endocervical canal may be at least as long and usually longer than the endometrial canal. The greatly enlarged portio vaginalis becomes roughened and the epithelial layer much thickened. As the unattended prolapse continues, the epithelial covering of the portio breaks down and if not already infected, chronic cervicitis ensues.

With a prolapsed uterus there are generally associated vaginal relaxations of all the walls to some degree. The accompanying defects are well known and need no discussion here. The commonly associated cystocele leads ultimately to urinary retention, with cystitis and trigonitis. From upper urinary-tract studies

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may be seen the abnormal "kinking" of the ureter as it passes through the parametrium in a case of prolapse. The ureters tend to dilate, and hydro-ureter with (in time) hydronephrosis is not uncommon. Thus the upper urinary tract, being adversely affected by the abnormal ureteral position and the associated infection so frequent in the bladder, adds troublesome complications to the uncorrected prolapse.

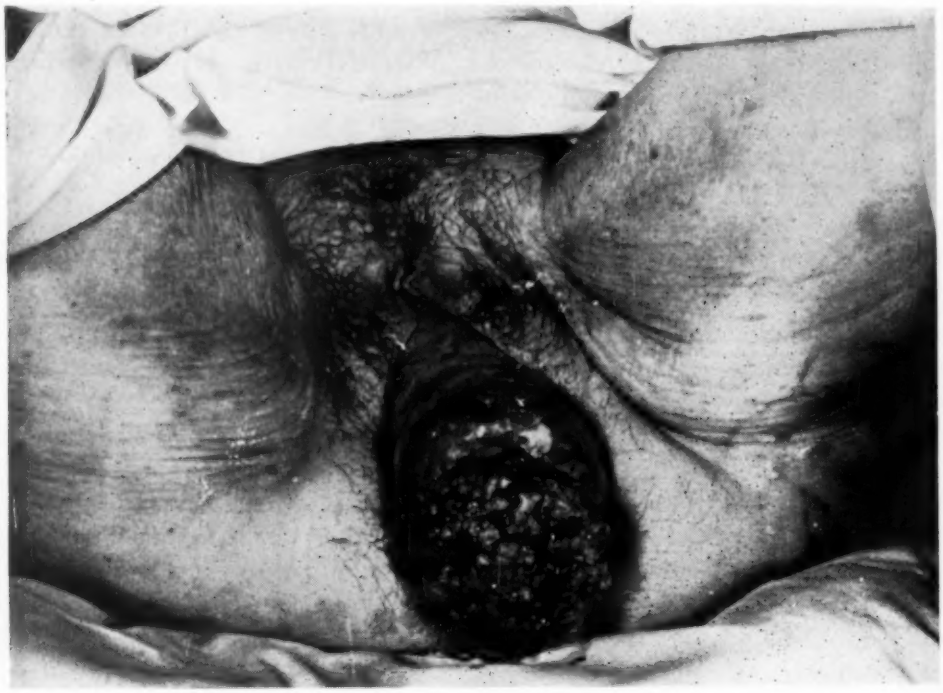

FIG. 1. Prolapse of the uterus with a rare complication: carcinoma of the cervix.

SYMPTOMS

Most often, prolapse sufferers come to the physician complaining of "something coming down" in the genital region. With a pure uncomplicated descensus that is the only complaint; but as so often happens, various complications are associated, such as severe chronic cervicitis, cystourethrocele and rectocele. All of these add in their own way to the complaints of the patient.

TREATMENT

It was quite common in the past for women in middle life or slightly beyond, to be told for no other reason than their age, that they could not "stand" an operation. Various types of pessaries were devised and unfortunately used. This type of medical advice is not given to patients today.

The first consideration in many of these patients is their age; however, we have found out long since that *age per se* is no contraindication to surgery, particularly the type needed to correct prolapse.

In the older age group there is no question that we must cope with the degenerative diseases and almost every conceivable medical complication. I have noted that when an elderly woman comes to my office by herself, complaining of a prolapse, she is a safe patient for surgery. However, as in the case of every patient before being operated upon, she must have careful medical appraisal. A base line of body function and its alterations by any existing disease is a necessary guide to the surgeon and the anesthetist.

Some may feel that our advice and practice is quite radical in regard to the overall need for surgical correction of prolapse. It is so long since I have fitted or advised a pessary for prolapse that it is beyond recall. I have not regretted operating upon these women and there have been no deaths. The rewarding gratitude from the patients is heartwarming. By comparison, I have seen patients, thoroughly "sold" twenty to thirty years previously by a doctor now deceased that they "could not stand" an operation, being helped into the office by none-too-patient nurses, friends or relatives, to have a malodorous pessary removed, cleaned and reinserted. The care of women with prolapse treated by a pessary over too long a time, is difficult. It is almost impossible to keep the vagina and pessary clean and the vaginal epithelium free from maceration. We seriously doubt that most patients cannot be safely operated upon when prolapse first occurs.

The choice and administration of anesthesia is best left to a physician anesthetist. Saddle, low spinal and caudal seem to be the methods most commonly used in these patients by the anesthesia department at Temple University Hospital. Pudendal and/or local infiltration are excellent choices but have the disadvantage of not relieving pain in the knees and hips. The older woman put up in lithotomy position needs anesthesia to hold such a position for any length of time.

Early ambulation in our institution refers to patients being on their feet twenty-four hours after surgery. In women over 70 years of age, this is too long to allow them undisturbed bed rest. Although, I may be accused of being heartless, I have such patients out of bed and in a chair for short intervals starting four hours after they come from the operating room. Thus these patients do not have a chance to lose their strength by inactivity and they have all the other advantages of early movement.

Surgical techniques applicable to the correction of uterine prolapse are many and varied. To be successful, however, there are a few principles that must be adhered to. First, an abdominal approach for the correction of prolapse is rarely if ever indicated. We still see cases of recurrent prolapse that have been treated by an amputation of the hypertrophied cervix and an abdominal suspension of the corpus uteri. All that happens when this operation is performed is that the cervix hypertrophies again until it is once more completely prolapsed. Plicating the cardinal ligaments in front of the cervix, along with the usual anterior and posterior vaginal plastic procedure is the operation of choice. Many surgeons, including myself, prefer treating prolapse after the childbearing period and then by vaginal hysterectomy and vaginal plastic repair.

Corrective operations for prolapse sometimes are improperly performed, so that coitus becomes either impossible or very painful. Occasionally surgeons assume that elderly women do not have intercourse and neglect to discuss the matter with the patient before surgery. Such instances have brought much unhappiness into the life of elderly persons. The gynecologist should never assume that any given patient is not cohabiting, regardless of age and infirmity. From the history of many elderly, happily married couples, I can only conclude that the sex act is enjoyed by well adjusted people until they die. For this reason, I rarely employ the Le Forte colpoclysis technique.

A discussion of technique is redundant, since every gynecologist performs the various operations in a slightly different manner from the model operation he is trying to duplicate. As time goes on, each operator has his own procedure and whether it is better or worse than the next man's is immaterial, as long as the basic idea of parametrial fixation is kept firmly in mind.

THE PERFORATED CRUCIATE INTRAMEDULLARY NAIL: PRELIMINARY REPORT OF ITS USE IN GERIATRIC PATIENTS

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Since the introduction of the intramedullary nail (1) in fracture fixation, this procedure has achieved acceptance and frequent use in open reductions. Particularly in the care of geriatric patients this method promised rapid mobilization of fractured limbs. Often the cumbersome cast could be omitted. Early motion prevented the disuse atrophy and joint stiffening common with previous methods of fixation. Osteoporosis, the result of prolonged bed rest, was minimized and the incidence of thrombophlebitis reduced (2).

As clinical evidence accumulated, some difficulties and limitations of this method became apparent (3). It is our purpose to demonstrate a new perforated cruciate type of intramedullary nail which allows wider application, possesses several obvious advantages and has fewer limitations. The perforated cruciate nail can be inserted through a single incision over the fracture site and may be positioned without x-ray control at operation.

METHODS

On cross section, the cruciate nail resembles an x-beam. The axis of the nail is perforated by a series of small holes, which are designed for levering and transfixion (Figs. 1, 2, 3 and 4). Made of 18-8 S.Mo. alloy, the cruciate nail possesses marked rigidity. Tests made in a metallurgic laboratory proved it to be stronger than a similar segment of the Kuentscher nail.

After the aseptic precautions generally used prior to bone surgery, such as a 24-hour skin preparation, an incision is made over the fracture site. A small hole is drilled into the bone near the fracture. Using the pilot of a cylindrical reamer as a guide, a button of bone is removed. One fractured bone-end is angulated and the cruciate nail inserted into the marrow cavity. The fracture is now reduced and the nail is positioned across the fracture site. This is accomplished by inserting a lever through the fenestration and engaging the holes of the cruciate nail to position it by simple lever action (Figs. 5, 6 and 7). The levering action is positive and gives accurately controlled action. The midpoint of the perforated cruciate nail is easily centered at the fracture site. This is done by counting the number of holes that pass the fenestration. When half the number of holes has passed the window, the ends of the cruciate nail are equidistant from the fracture site.

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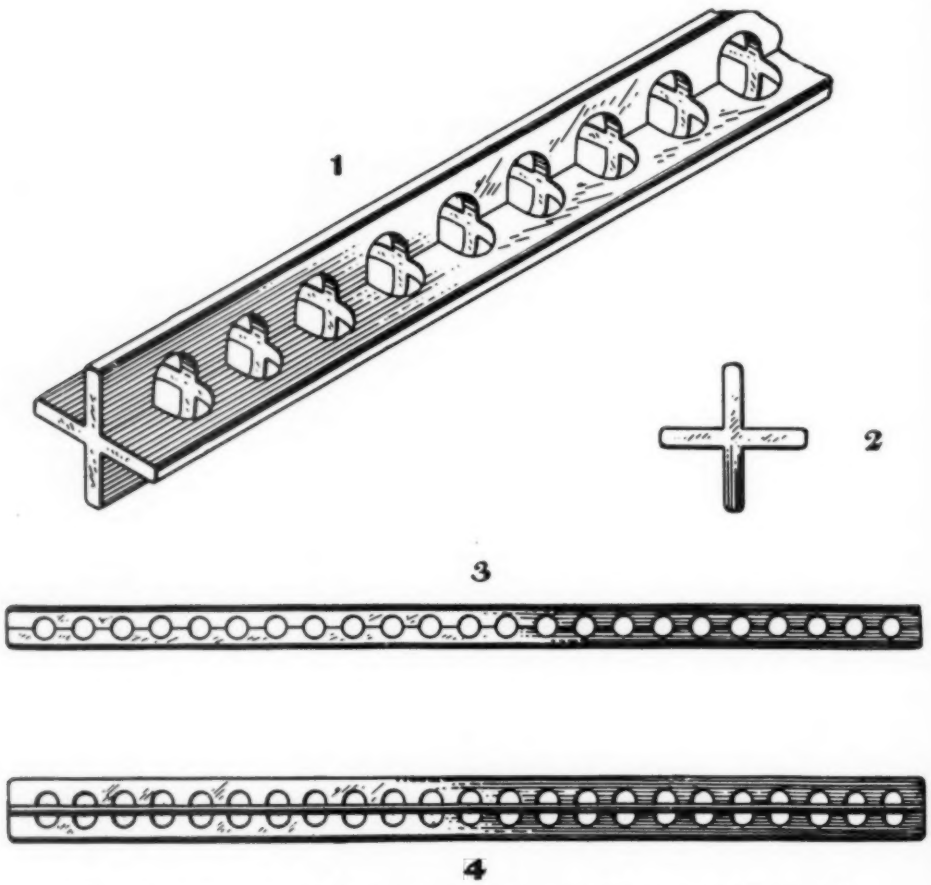
The small button of bone is then replaced. An ordinary 18-8 bone screw is inserted through the bone button, and through the perforated cruciate nail into the opposite cortex. By its "cross bolt" effect, this screw prevents migration or "wandering effect" of the intramedullary nail.

Levering the nail into position can be accomplished easily and gently. This gentle action is in marked contrast to the more violent technic of hammering the ordinary nail into position. Kuentscher (4) measured the pressure exerted



FIGS. 1, 2, 3, and 4. Various views of the cruciate intramedullary nail.

on the marrow contents by hammer blows. He found that it far surpassed normal blood pressure, and theorized that it might cause fat embolism. Ease of insertion of the perforated cruciate nail should minimize this danger.

In order to obtain a close fit of the cruciate nail in the marrow cavity, it may be necessary to enlarge the cavity with a simple rod-like reamer (Figs. 8 and 9). This is of value in correcting the normal curvature that frequently exists. The reamer is of the same diameter as the cruciate nail and is calibrated with one-inch circular grooves with which to judge the depth of insertion (Fig. 13).

In comminuted fractures the comminution provides the opening through which

the cruciate nail can be manipulated. The comminuted fragment is then replaced. It is fixed in a similar manner through the cruciate nail to the opposite cortex by a bone screw (Fig. 10).

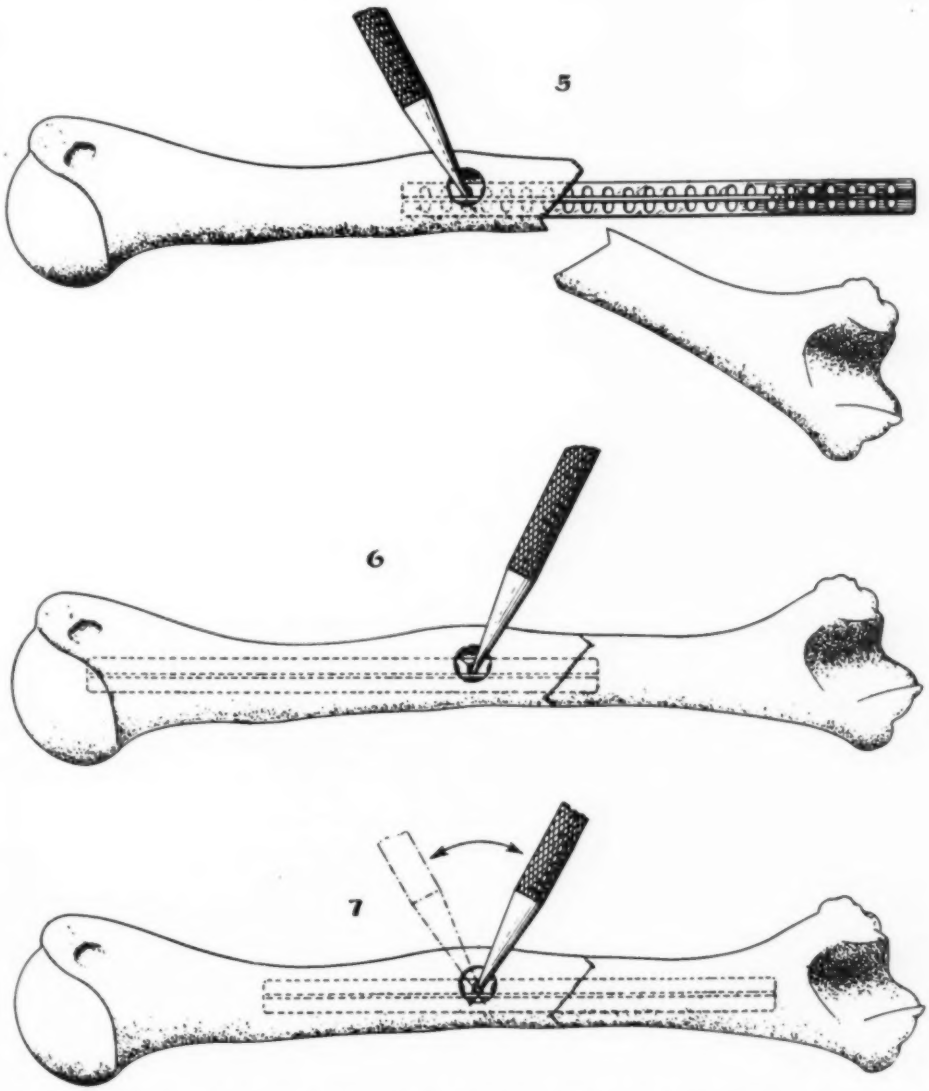


FIG. 5. The lever is inserted through the fenestration in the bone and into the holes in the cruciate nail. Nail may be inserted in retrograde direction by either the lever or a mallet.

FIG. 6. Reduction of fracture accomplished and nail moved into position by manipulation of the lever.

FIG. 7. Nail now in final position and fixation completed.

In transverse fractures which are directly perpendicular to the shaft of the femur, after fixation with the smooth Kuentscher nail, torsional strains are frequent. With the cruciate nail, on the other hand, the four fins tend to prevent

rotation. Also, both ends of the cruciate nail may be affixed to the bone. This, however, would prevent the desired impaction of the bone ends at the fracture site. Thus the action would be similar to an ordinary bone plate, although in effect this bone plate would be within the medullary cavity.

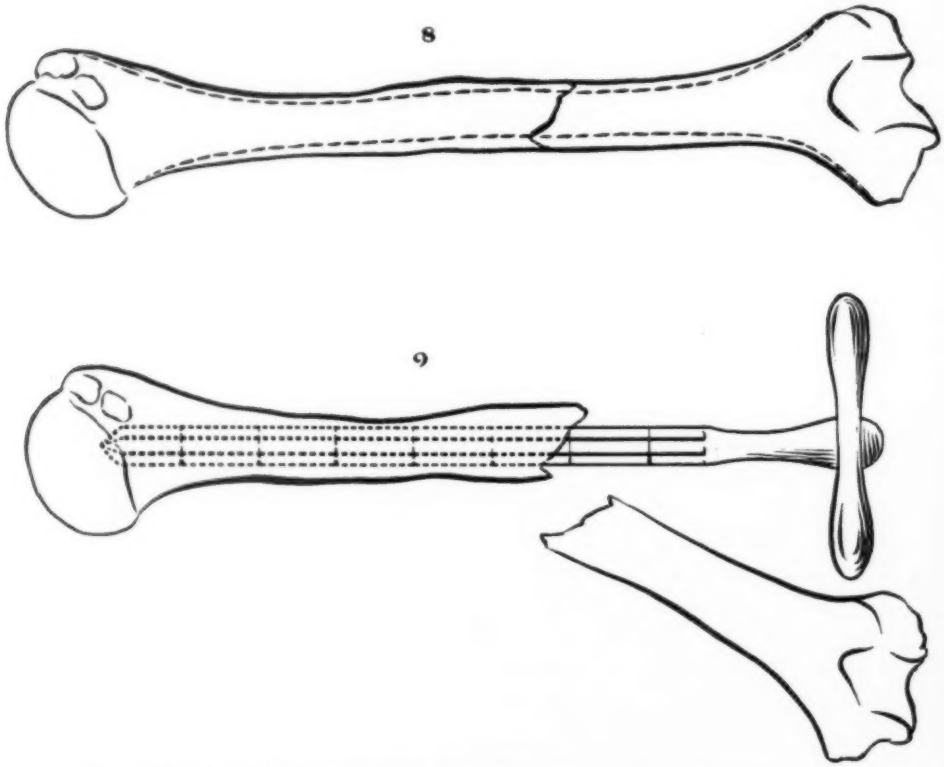


FIG. 8. Fractured humerus with schematic illustration of marrow cavity.
FIG. 9. Simple rod-like reamer which may be used to widen or straighten the marrow cavity for more accurate fit of the cruciate nail.

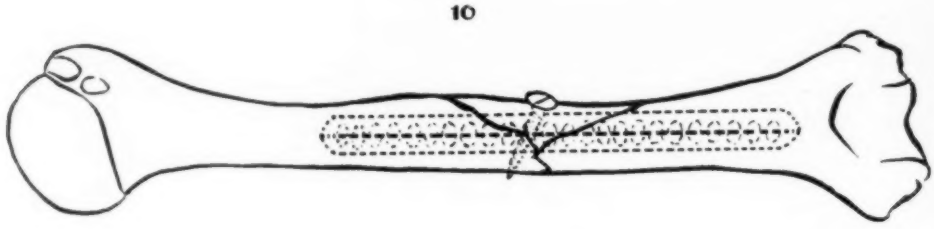


FIG. 10. Showing use of the cruciate nail in a comminuted fracture of the humeral shaft, and method of transfixing fragment to the opposite cortex.

The marrow cavity is normally larger at both ends of the long bones. In osteoporotic bone, the entire medullary cavity is enlarged and the cortex is thinned. The enlarged ends of the marrow cavity in both normal and osteoporotic bone make solid fixation with the ordinary nail difficult in fractures in this area. A

completely rigid fixation of the cruciate nail in this widened area may be easily accomplished. Two screws at right angles to each other are used to transfix the cruciate nail. This results in complete immobilization of the nail within the widened portion of the marrow cavity. This feature is highly desirable in elderly patients with osteoporosis.

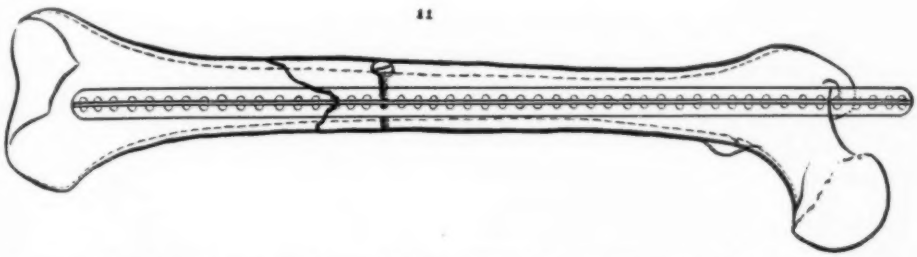


FIG. 11. Showing four-finned, cruciate nail used in the Kuentscher manner in a fractured femur. The "cross-bolt" screw prevents migration of the nail and impaction still occurs at the fracture site, by muscle pull. This screw and nail can be extracted readily.

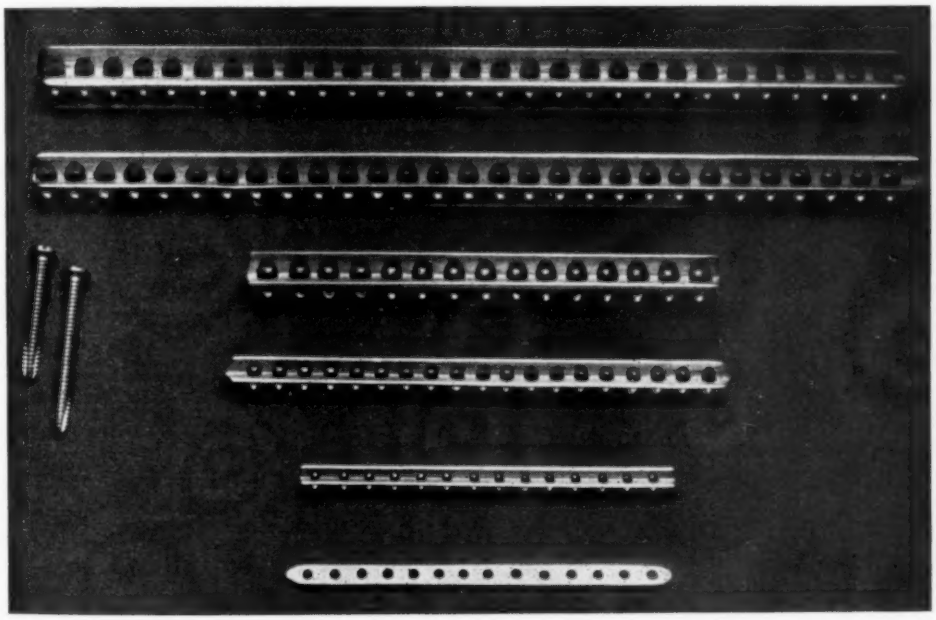


FIG. 12. Various sized cruciate nails and screws formed of 18-8 S.Mo. alloy. The lowest nail is flat and flexible and is proposed for use in the clavicle.

In fractures of osteoporotic femurs, as many as two or three nested Kuentscher nails have been necessary for fixation. The nails must be forcibly driven into the marrow cavity. This method is complicated and introduces a large amount of metal.

A modification which we have contemplated consists of a long, perforated cruciate nail. This could be used in the same classic manner as the ordinary

Kuentscher nail. The "cross bolt" effect would still prevent migration or "wandering" of the nail and it could be extracted readily in routine manner (Fig. 11).

A further modification that we are considering, but have not employed clinically, consists of a small flat perforated flexible nail (see at bottom of Fig. 12). This nail may be employed in immobilization of a fractured clavicle. The technic would permit adaptation of the nail to a markedly curved marrow cavity. The aperture for positioning could easily be formed at the fracture site with a rongeur.

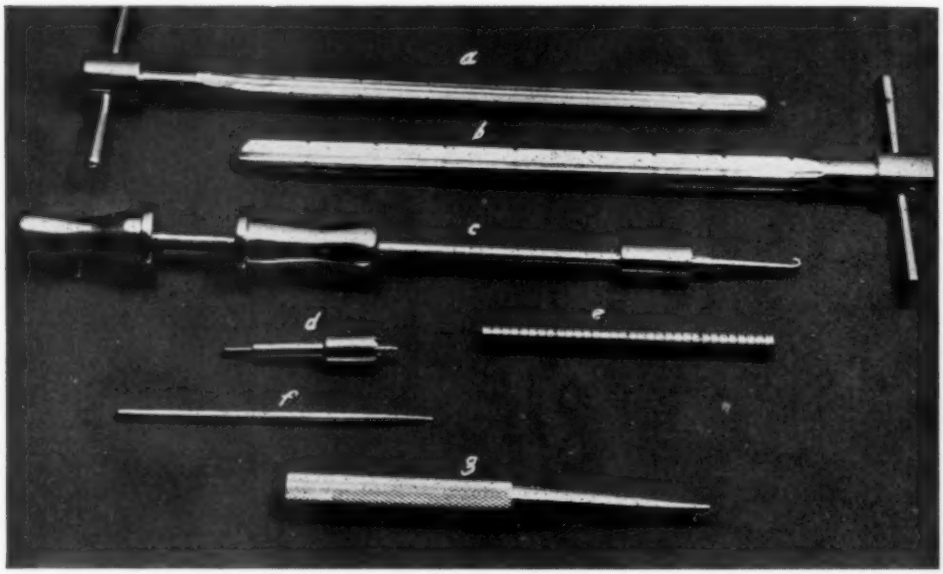


FIG. 13. *a* and *b*: Two rod-like reamers marked along their lengths by one-inch circular grooves. *c*: Regulation nail extractor modified to fit the cruciate nail. *d*: Simple cylindrical reamer with pilot for forming the window. *e*: X-ray measuring rod with $\frac{1}{8}$-inch grooves, to be used preoperatively to gauge size and length of marrow cavity. *f* and *g*: Simple levers for positioning cruciate nails.

CLINICAL APPLICATIONS

Case 1

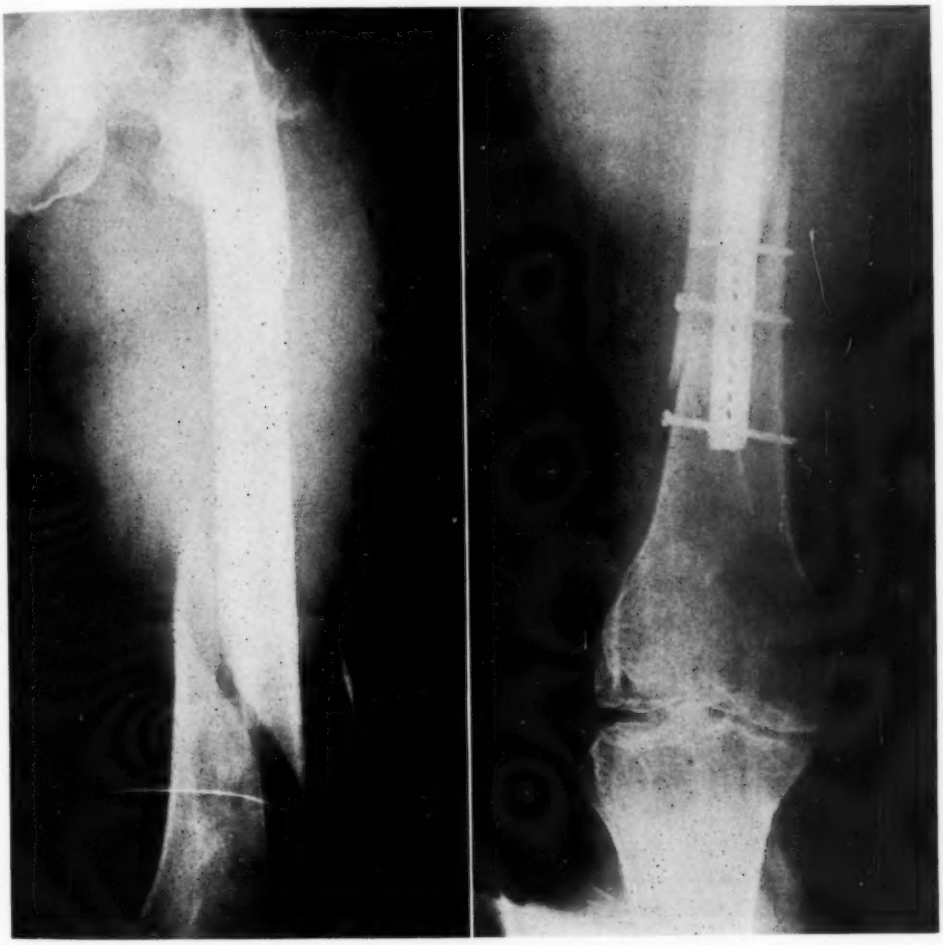
A: This 83-year-old female had a spiral fracture in the distal third of the femur (Fig. 14 A). Approximately a decade previously, she had had an intertrochanteric fracture, which healed well. Because of this slight deformity, the question was raised as to whether use of the Kuentscher nail was advisable.

B: Osteoporosis had markedly enlarged the marrow cavity; therefore, a large .65-inch diameter cruciate nail was employed. The nail was inserted into the proximal fragment and levered across the fracture site. Three screws passing through the cruciate nail were used to immobilize the fracture. X-ray examination (Fig. 14 B) showed imperfect reduction, but at operation fixation was rigid.

Case 2

A: This 54-year-old white female had complete nonunion of the neck of the humerus, of eight months' duration. A previous attempt at fixation with a spline was unsuccessful. There was marked osteoporosis (Fig. 15 A).

B: The cruciate nail was inserted into the distal fragment, reduction was accomplished and the nail levered into the proximal fragment. Both fragments were immobilized by the longer screw seen in Figure 15 B. An autogenous iliac bone graft was secured across the fracture site by two additional screws. These were transfixed through the cruciform nail into the opposite cortex. The limb was immobilized solely with a Velpeau bandage. Eight weeks later, circumduction exercises were started.



A B

FIG. 14. Case 1.

Obviously, the perforated cruciate intramedullary nailing technic is adaptable to the younger age group.

Case 3

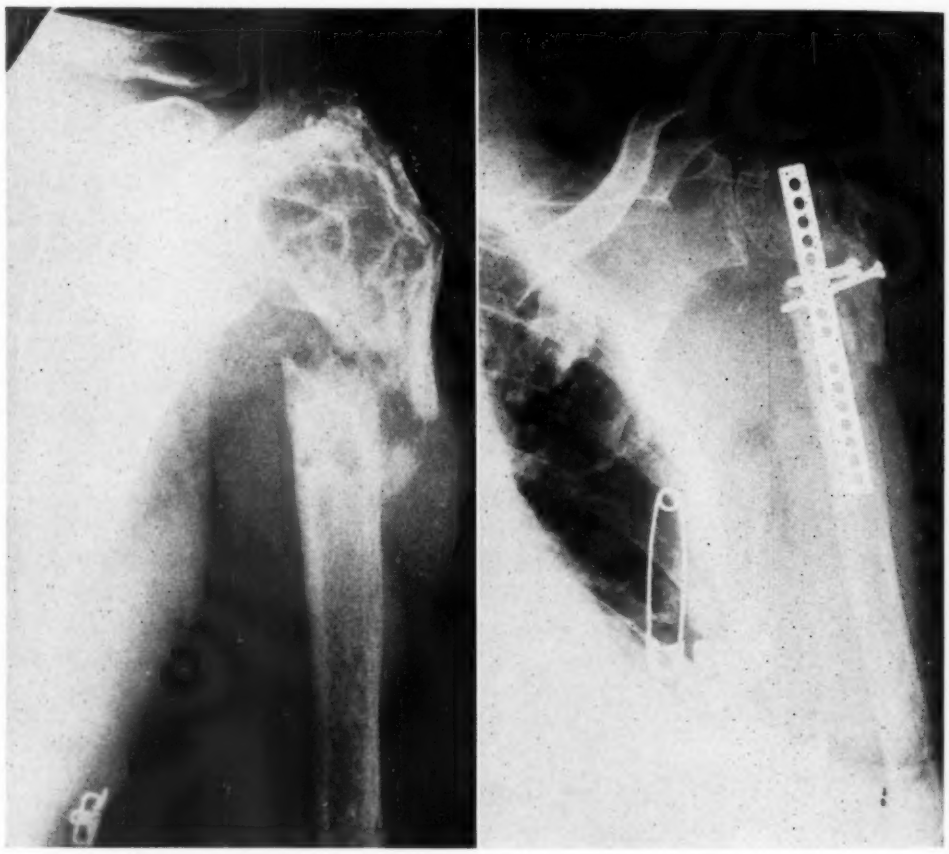
A: This 28-year-old white male had a comminuted fracture at the juncture of the middle and lower thirds of the tibia and fibula (Fig. 16 A).

B: Since the marrow cavity in this portion of the tibia was triangular in shape the cavity was reamed prior to insertion of the cruciate nail. The nail (equal in diameter to the reamer) was inserted into the proximal portion, the fracture reduced and the nail

levered into position across the fracture site. One screw was used to transfix the tibial comminution. Rigid fixation was obtained because of the close fit of the cruciate nail in the marrow cavity (Fig. 16 B).

Advantages of the perforated cruciate nail

1. The "wandering" frequently observed with the Kuentscher nail is eliminated by the "cross bolt" effect obtained with the transfixing screw and the perforated cruciate nail.



A B

FIG. 15. Case 2.

2. The cruciate nail requires only a single incision over the fracture area. No counter incision is needed for insertion.

3. The cruciate nail does not extend beyond the marrow cavity or into the soft tissue.

4. It may be used in comminuted fractures.

5. It is light in weight and strong. Under stress tests in a metallurgic laboratory, it resisted greater force than a similar segment of the Kuentscher nail.

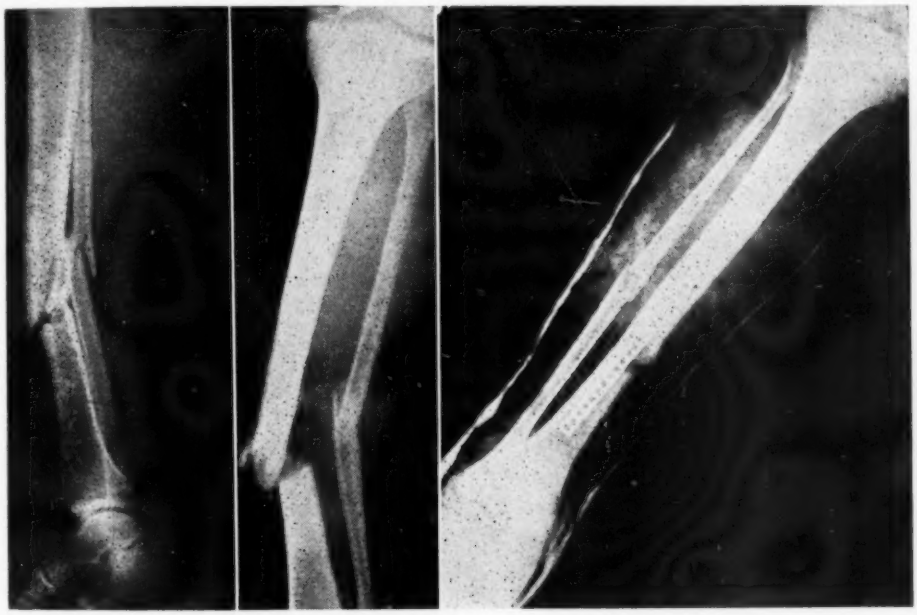
6. It can be used in conditions other than fracture fixation, *e.g.*, nonunions, treatment of massive bone cysts and in conjunction with bone grafts.

7. Its girder-like construction results in less encroachment on the marrow cavity than do the arcuate Kuentscher or the diamond-shaped Hansen-Street nails. Therefore, endosteal healing is probably more rapid.

Disadvantages of the perforated cruciate nail

1. The obvious and serious disadvantage is in the removal of the cruciate nail, should that become necessary. In a nonunion, this could be accomplished through a long, sliding bone graft.

2. The longer length of the Kuentscher and Hansen-Street nails makes them more adaptable for use in femoral fracture fixations.



A B

FIG. 16. Case 3.

DISCUSSION

In discussing intramedullary nailing, Eaton (5) comments, "The older the patient and the more prolonged the anticipated convalescence, the more is the physician justified in submitting the patient to intramedullary nailing."

Although the importance of early ambulation to the geriatric patient can hardly be overestimated, there are other considerations. There should be emphasis on reduced pain, simpler after-treatment, and greater comfort to the patient. All of these factors add up to higher morale. When there is early motion, muscles remain in tone, joint stiffening and disuse atrophy do not occur, and the incidence of postoperative pneumonia and thrombophlebitis is reduced. Frequently, with intramedullary nailing, no cast is necessary. Because of shortened hospital stay, expenses are minimal.

The technic of intramedullary nailing is relatively new. Sufficient time has

not elapsed to permit long-term evaluation as to the ill effects, if any, resulting from temporary or permanent inclusion of a metallic body in the marrow cavity.

Analogies may be drawn from other metallic foreign bodies that, by design or accidentally, have been introduced and retained within the body. Vitallium and 18-8 S.Mo. prostheses have been used without apparent toxic effects. Providing the metal resists corrosion, no undue difficulties seem to have been encountered.

A thorough search of the available literature on intramedullary nailing has revealed no instance of toxicity from retention of the nail within the marrow cavity. Patients have frequently refused to have the nails removed. In these cases, 28-month follow-ups have not revealed any ill effects from retention of the nails (6).

McMunn (7) and Berry (8) reported that the presence of intramedullary nails does not seem to have caused any disturbance in hematopoiesis. Except for noting a transient eosinophilia, Kuentscher (4) made similar observations. Another study (9), in which blood examinations were made at five-day intervals for a period of six months after the fracture, showed a rise of from 10–30 per cent in hemoglobin level and red cell count.

SUMMARY

Intramedullary nailing with the Kuentscher technic has been advantageous to elderly patients with fractured femurs. Presentation is made of a new-type, perforated cruciate intramedullary nail. This cruciate nail possesses several advantages:

1. No wandering effect.
2. Single incision.
3. Easier insertion.
4. Complete containment within the medullary cavity.
5. Less displacement of medullary tissue.

Three case histories are presented.

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Editorial

BRONCHIOGENIC CARCINOMA

It is becoming increasingly evident that lung cancer is the most common visceral carcinoma in the male. The general increase in cases of carcinoma, compatible with a larger proportion of the population reaching advanced ages, partially explains the increases in carcinoma of the stomach, rectum and other organs. During this same period, however, lung cancer, once thought to be relatively rare, now exceeds these other common cancers roughly in a ratio of five to three.

A complete and unqualified explanation for the alarming increase of bronchiogenic carcinoma is not available. The statistical studies of Wynder and Graham[1] and others strongly incriminate cigarette smoking. On the other hand, the unexplained small group of cancer victims who have never used tobacco in any form remains a puzzle. It must be noted, however, that the case against the cigarette is sufficiently strong to cause prominent interested members of the medical profession to either abandon smoking or resort to a variety of apparatuses containing filters, in hope of protection.

For prospective victims of advanced or middle age, abstinence or the use of smoke filters offers little assurance against lung malignancy, since it appears from statistical studies that a history of heavy smoking in early years, even if the habit has been discontinued for some time, may account for some cases of bronchiogenic carcinoma.

The subject of lung cancer was only of academic interest, until 1933. Fortunately, the right surgeon and a suitable subject made possible the first cure. Evarts A. Graham removed the entire lung of a medical colleague. Now, twenty years later, the patient is well and continues in productive practice. Only two people can know the courage required of both parties.

During the twenty years following the first successful operation for lung cancer, the field of chest surgery has improved tremendously. Not only technical advances, but perfection of anesthetic technics, the availability of antibiotics, the use of blood transfusions, and the knowledge of fluid balance, have made lobectomy and pneumonectomy as safe as major operations elsewhere in the body. Mortality and morbidity compare favorably, provided the patient has sufficient pulmonary reserve. In this connection two important facts must be considered: first, chronologic age; and second, but more important, physiologic age. The considerations for lung surgery in the older age groups must involve careful evaluation of both lung and cardiac capacity.

Cancer patterns vary, but usually the older age group is afflicted with an indolent, well differentiated type of neoplasm. In these instances, valuable palliative surgery may be possible. A spry, 80-year-old patient may stand a palliative

[1] Wynder, E. L., and Graham, E. A.: Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma, *J.A.M.A.* **143:** 329 (May 17) 1950.

lobectomy; but a patient aged 60 or 70, a reasonably good risk, may die six weeks to six months following pneumonectomy because his heart will not tolerate the physiologic impact of the loss of an entire lung.

Factors of safety decrease sharply as the aging process continues. The treatment of lung cancer in the older age group, therefore, must be individualized. Early detection by the use of biannual x-ray examination of the chest may direct attention to the lesions months or even years before clinical symptoms become apparent. Surgical procedures, if undertaken, must be planned in accordance with the pulmonary reserve, the location of the tumor and predictable life span.

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The George Washington University School of Medicine,
Washington, D. C.

Current Geriatric Literature

SUPPURATIVE ARTHRITIS IN THE AGED.
R. D. Blachford.
Lancet **1**: 26, 1953.

Degenerative disease is so often found in the aged that its presence is apt to be assumed by the physician. This assumption leads easily to the further assumption that, if it is possible to explain any symptom in an old person in terms of a degenerative process, that explanation will probably be correct. However, probability is not certainty, and various diseases masquerade as arteriosclerosis, cerebral thrombosis, or cardiac failure. Several cases of patients aged 69 to 87 are described, in which stroke had been diagnosed. However, at necropsy it was found that the patients had been suffering from suppurative arthritis. Data in the literature show that among suppurative joints, the shoulder is not a rarity. It has been observed especially in the aged. Apart from gonococcal disease and penetrating wounds of the joints, suppurative arthritis is usually pneumococcal. It may be associated with osteomyelitis as well, in which instance it is usually staphylococcal. In the cases under consideration, the sources of infection were the lungs, the teeth and an ulcer on a toe, respectively; in all the patients weakness and inability to use one arm was present. However, it is not suggested that joint suppuration is a common cause of uselessness of the arm. The author's point is that such suppuration may occur in aged people and can be missed. When a swollen joint is seen in such a patient, the presence of pus should be seriously considered.

THE EFFECT OF SURGERY ON LIFE REALIZATION OF ADVANCED AGE GROUPS.
Byrd, Benjamin F., Jr.
Am. Practitioner **4**: 25, 1953.

Byrd noted that surgery can offer more and more to the older person—by maintaining a healthy, profitable, comfortable, long life. The case of a 75-year-old man is described. The patient had cardiac decompensation with a blood pressure of 200/100. An arteriovenous fistula in his posterior tibial artery was found. The old man remembered that he had stuck himself with a tobacco knife when he was 17. When the fistula was closed the patient was well, the decompensation was controlled and the blood pressure was 120/74.

Comment: Old people stand surgery well, as in the case of a 57-year-old man with a blood pressure of 300/120 who was operated on for prostatectomy recently. In Byrd's case the history of the man stabbing himself is of great importance. That alone would make one look for an arteriovenous fistula. Unfortunately, few take the time to examine the patient sufficiently to detect such abnormalities.—*M.W.T.*

THE GERIATRIC PROBLEM IN MENTAL HOSPITALS.
L. C. Cook, E. Cunningham Dax and W. S. Maclay.
Lancet, **1**: 377, 1952.

In 1938 there were 23,000 patients aged 65 and over in public mental hospitals of Great Britain and ten years later, 31,000. In spite of this, mental hospital beds were reduced as a result of war conditions, by over 3,000. Whereas in the United States the aged with mental aberrations are sent to mental hospitals, in Europe they used to be placed in special institutions for the aged, or cared for in the community. Diminished accommodations in special institutions and less care in communities during recent years explain the pronounced changes in the 1948 curve. Since the erection of new buildings is prohibited by the economic and labor situation the authors suggest the following:

More advice should be available to general practitioners in the care of this type of pa-

tients, particularly in more practical use of sedatives. This is to be done by domiciliary visits, appointing more geriatric officers and better training of medical students in geriatrics.

More use is to be made of psychiatric social workers in persuading families to look after their own kin, educating them in their responsibilities.

More practical use should be made of health visitors, district nurses, and other assistants. Geriatric medical officers should help general practitioners with advice on the management and disposal of senile patients.

Hospitals or institution wards, closed for lack of nurses, should be attached to teaching hospitals and reopened for geriatric patients. Units for geriatric patients should be an integral part of main hospitals. It should also be a part of the general nurses' ordinary duties to be posted there in their turn. All student nurses should spend part of their training in a geriatric unit.

The maximum number of beds should be available in old people's wards.

HISTOLOGIC CHANGES IN THE AGING COCHLEA.

W. P. Covell.

J. Gerontol. **7**: 173, 1952.

Histologic examinations were made of the cochlea of the ears in aged subjects with severe nerve deafness. They failed to demonstrate a close relationship between structural changes and the degree of hearing loss.

Histologic evidence for loss of hearing high tones with advancing age is not definite. Thorough understanding of factors producing nerve deafness at different ages is required before old age can be said to be a single factor. However, there is no doubt that mental processes become slowed with age.

Not all old people show the same degree of hearing impairment. Hormonal factors have been said to be the contributing factors; but sufficient evidence is lacking. Vascular pathology also causes hearing impairment; this is to be correlated with advancing age to some extent. However, it does not wholly explain the prevalence of hearing loss commonly associated with aging.

The offspring of a mother who had German measles during early pregnancy has been shown to suffer from nerve deafness. Another cause for it may be the incompatibility of the Rh factors, with the production of erythroblastosis fetalis in the infant.

Controlled experimental animal studies, in which hearing can be evaluated by physiologic and histologic methods, offer an approach to the problem.

THE ARTERIAL LINING.

J. B. Duguid.

Lancet **2**: 207, 1952.

Tentative interpretations of the pathogenesis of atherosclerosis and hyaline arteriosclerosis have been made. They show that the orthodox views are by no means the only possible ones. In the past, views on arterial disease have been limited by a traditional notion, *i.e.*, that all new tissues are products of pre-existing cells. It has been stated that any increase in thickness of vessels signified swelling or proliferation of its tissues. We now recognize that extracellular tissues are not necessarily subject to any such law. The fact is that arterial lining is a labile structure. This makes it possible for solid matter forming in the blood-stream to be added to the body tissues. According to the author, this has been proved beyond any shadow of doubt.

AURICULAR FIBRILLATION IN THYROTOXICOSIS, WITH SPECIAL REGARD TO THE INDICATION FOR QUINIDINE THERAPY.

A. Jervell.

Acta med. Scandinav. suppl. 266: 585, 1952.

Of 279 cases of thyrotoxicosis under observation, auricular fibrillation was recorded in 53 instances. Auricular fibrillation occurs mostly in older age groups. The thyrotoxic con-

dition must be treated first. Before this is done, quinidine treatment is contraindicated. If fibrillation persists after thyrotoxicosis has been brought under control, quinidine therapy may be considered. In older patients (aged 60 to 70) and in fact in any patient with distinct hypertrophy or electrocardiographic signs of a myocardial lesion, the question must be decided individually. In such cases the patient should be kept under constant observation, in order to study subjective inconveniences and complications. In patients over 70 and all other patients with considerable hypertrophy of the heart, quinidine therapy is contraindicated. In these instances the danger of toxic effects from quinidine is relatively great.

SOME PRACTICAL CONSIDERATIONS IN THE CARE OF THE OLD
N. H. Nisbet.
Lancet **1:** 184, 1953.

The task of rehabilitating old people is never easy. It is particularly difficult when they have lain neglected in an old "chronic" hospital. However, it is most rewarding work. At first the difficulties seem to be insurmountable because of the opposition of the diehards and the fears and the conservative attitude of the nurses. The frail condition and physique of the patients, and the unsuitable nature of the traditional "bedridden wards" are other obstacles. Only the knowledge of similar difficulties overcome elsewhere and the spectacular results achieved, give the beginners courage to go on. When the first tentative steps are made, progress is naturally at a snail's pace. The patient is helped out of bed and put in a chair for ten minutes. The aged individual may slip off and has to be put into bed again hastily. Next day the patient may seem more lively, but the crooked knees give new cause for despondency. Yet the effort is worth while, for at worst the aged person may be taught to get about in a wheelchair. Then the patient can be greatly improved by remedial exercises and may succeed in walking again unaided. The Balkan beam is used, bed exercises are begun and a few steps are taken pushing a chair. Sometimes the aged patient is launched with the help of a walking-machine, then proceeds to two Warral sticks, and finally gets along with just a plain walking stick with a rubber end. All this is slow and laborious for patients, nurses and doctors, and there may be little perceptible change each day. However, a year later the transformation may be startling. Then the hospital has ceased to be a stronghold of apathy and gloom.

In the beginning of treatment, the Brocklehurst bed is often used. It accepts incontinence as incurable and makes a virtue of immobility. Senile patients with fecal incontinence can be treated with a regular weekly enema. It may, however, require several weeks before the benefit is apparent. Regarding urinary incontinence, in the male patient, the urinal can be strapped between the thighs. This may lead to excoriation of the skin if not washed often enough. Incontinence appliances for old women are usually unsuccessful. Patients of either sex may find the bedside commode easier to use than the bedpan. The urinal holder described by Ingham should be more widely used.

PATHOLOGICAL ANATOMY OF SENILE AND PRESENILE DEMENTIA. (Pathologische Anatomie der senilen und presenilen Demenz.)
F. Seitelberger.
Wien. klin. Wchnschr. **64:** 856, 1952.

Following general characterization of senile involution of the brain, histopathology of senile dementia is described. In this stage different forms of gradually increasing damage of ganglion cells are found, due to old age. So-called pigment atrophy also occurs in aged people, through which condition the cells are repleted with lipofuscin. The most characteristic sign is, however, the development of argentophil (argyrophil) plaques in the cerebral cortex and in certain basal ganglia. Another typical sign is intracellular change of the neurofibrils. In cases of Alzheimer's presenile dementia, similar morphologic substrata are present. The foregoing process is observed to a high degree in the parieto-occipital area of the cerebral cortex.

In Pick's disease, pronounced circumscribed systematic atrophy of the brain develops.

It affects the frontal and temporal areas, causing increased firmness in the shrunken portions of the brain. From the histologic point of view, marked deficiency of ganglion cells, damaged cells, loss of myelin and cerebellar fibrogliosis are found. Changes in plaques and fibrils are rather rare occurrences.

AGING OF NEUROFIBRILS.

J. M. Sosa.

J. Gerontol. **7:** 191, 1952.

Histologic changes in tissues of the human central nervous system occurring with increasing age are described. This is a special change of the neurofibrillar network; it is related to the accumulation of lipochrome pigment (lipofuscin) in the cytoplasm. This process is designated as lipochrome neurofibrillar or lipofuscin neurofibrillar degeneration.

It begins with dissociation and agglutination of the neurofibrils and ends with total neurofibrillolysis. There are three distinct stages of the degenerative process. The pigment accumulation generally is marked in the nerve cells of old persons. The intensity and extension in the areas involved apparently increase with age.

Since lipochrome neurofibrillar degeneration is found with such frequency in nerve cells of old people, it apparently is an aging process.

NOTES ON GERIATRICS.

M. W. Thewlis.

Med. Times **80:** 368, 1952.

The preclinical preventive geriatric period extends from the ages of 20 to 40, during which period patients are conditioning themselves for disease. At that time prevention of diabetes, peptic ulcer, and arterial hypertension is as necessary as it is at 70 or 80. Surgery becomes often indispensable in the aged, who mostly withstand surgery well enough. However, the physician should give the standard treatment of disease at maturity instead of senescence.

Obesity when associated with heart disease or kidney distress may become dangerous. In most cases correct nutrition will keep weight at a normal level. High fat intake contributes to arteriosclerosis. Adequate proteins, such as in meat or fish, are important. Nevertheless, a supplementary diet of millet and sunflower seeds, containing amino acids, calcium and vitamins, is advisable.

"Arteriosclerosis" is an easy dismissal for "uncertain" ailments in the aged. Old people should not be frightened by such words as arteriosclerosis, shock or arthritis. The aged attach exaggerated importance to high blood pressure and are unduly sensitive about it. Hypertension does not necessarily lead to cerebral accidents. However, the senile organism is delicate and must be handled with care. A good geriatrician is gentle with his old patients. He does not place the accent on old age. After all, most of the rather few geriatricians are too pessimistic.

X-RAY THERAPY IN RETINOPATHY.

R. H. Trueman, J. T. Beardwood, Jr. and J. J. Smith.

Diabetes **2:** 13, 1953.

Intensive roentgen therapy was given in a series of cases of advanced diabetic retinopathy, characterized by retinitis proliferans and newly formed blood vessels extending into the vitreous. A total dose of 2,400 r was used in most patients; a few received 4,800 r. In 33 per cent of the eyes treated there was some degree of regression of the newly formed blood vessels and, to a lesser extent, of the retinitis proliferans, with some improvement of the visual acuity. These were advanced cases.

Until the cause of diabetic retinopathy is found, roentgen irradiation is worthy of a trial in the attempt to minimize the fibrous tissue proliferation and the increase in neovascularization, so disastrous to vision. Paulsen (*Diabetes* **2:** 7, 1953) hints that in young

patients with severe retinopathy, consideration might be given to some means of reducing the function of the pituitary gland or adrenal cortex.

Comment: Paulsen reported a diabetic woman in whom typical Simmonds' disease developed during pregnancy. The retinopathy gradually disappeared. Paulsen concluded that diabetic retinopathy is reversible; also that probably retinopathy is a consequence of metabolic disorder.—*M.W.T.*

EMPHYSEMA AND PULMONARY HEART DISEASE IN THE ROENTGEN PICTURE. (Emphysem und Cor pulmonale im Röntgenbild.)
F. Wachtler.
Wien. klin. Wchnschr. **64:** 906, 1952.

The symptomatologies of the different types of emphysema are shown in reproductions of characteristic roentgenograms of chronic, substantial, senile (emphysema due to senile dilatation of the alveoli pulmorum), and vicarious emphysema. It is emphasized that, contrary to the general opinion, it is by no means easy to diagnose emphysema. In certain cases a diagnosis cannot be made at all. Roentgenograms of acute, subacute and chronic pulmonary heart disease are shown as well. Cor pulmonale is not necessarily associated with emphysema. Through roentgenography it has often been possible to prove that in erroneously diagnosed cases of emphysematous cor pulmonale, not cardiac, but pulmonary insufficiency existed.

WINNERS OF SCHERING AWARDS TO MEDICAL STUDENTS

The three winners of the 1952 seventh annual Schering Award competition among medical students have been announced by Dr. M. William Amster, chairman of the award committee.

One award of $500 was presented to Edward Allen Jones, a sophomore at Meharry Medical College, Nashville, Tennessee, for the outstanding paper on "Steroid Hormones in Geriatrics." Selection of the best paper on this subject was made by Dr. Willard O. Thompson, clinical professor of medicine, University of Illinois School of Medicine, and editor of the Journal of the American Geriatrics Society.

The $500 award for the outstanding paper on "The Topical Uses of Antihistamines" was given to Seymour Cohen, senior medical student at the State University of New York at Syracuse. Dr. Frederick Reiss, professor of dermatology at New York University College of Medicine, was the judge for this subject.

Another $500 award went to William Howard Spencer, junior at the School of Medicine, University of California Medical Center, San Francisco. His paper on "Chemotherapy of the Eye" was selected as the most meritorious by Dr. Dan M. Gordon, assistant professor of clinical surgery, Cornell University Medical School.

The Schering Award seeks to encourage among the nation's medical students original reporting and exploration of recent developments in therapy, in the hope that they will later contribute to the general knowledge throughout the medical profession.

SECOND INTERNATIONAL CONGRESS OF CARDIOLOGY

The Second International Congress of Cardiology will be held in Washington, D. C., September 12–15, 1954. It will be immediately followed by the Annual Scientific Sessions of the American Heart Association, September 16–18, 1954. The opening session will be held in the auditorium of Constitution Hall at 10:30 A.M. on Sunday, September 12, 1954, with addresses of welcome. A reception will be given at the Mayflower Hotel at 5:00 P.M. on the same day for all Members of the Congress and their families. A banquet will be held September 15, 1954 at 7:30 P.M.

The Scientific Sessions lasting for three days will include formal papers, panel discussions, clinical pathological conferences and visits to important medical centers in Washington and Bethesda. The program will be printed in French, Spanish and English. Immediate translation of some of the papers and discussions will be made in three languages.

A series of Post-Congressional visits and conferences to at least 20 of the leading cardiac clinics in different parts of the U. S. and Canada has been arranged by special committees of local Heart Associations in the various cities.

L. W. Gorham, Secretary-General
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